Journal of
THE CHEMICAL SOCIETY

Committee of Publication

Chairman: Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.
J. S. Anderson, M.Sc., Ph.D., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
C. E. H. Bawn, B.Sc., Ph.D., F.R.S.
D. J. Bell, Sc.D., Ph.D.
R. P. Bell, M.A., B.Sc., F.R.S.
E. J. Bowen, M.A., D.Sc., F.R.S.
H. Burton, Ph.D., D.Sc., F.R.I.C.
A. H. Cook, D.Sc., F.R.I.C., F.R.S.
C. A. Coulson, M.A., D.Sc., F.R.S.
F. S. Dainton, M.A., Ph.D.
C. W. Davies, D.Sc., F.R.I.C.
H. J. Emeléus, D.Sc., A.R.C.S., F.R.S.
F. Fairbrother, D.Sc.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
H. R. Ing, M.A., D.Phil., F.R.S.
C. K. Ingold, D.Sc., F.R.I.C., F.R.S.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
F. G. Mann, Sc.D., F.R.I.C., F.R.S.
R. A. Morton, D.Sc., Ph.D., F.R.S.
L. N. Owen, Ph.D., D.Sc., F.R.I.C.
J. M. Robertson, M.A., D.Sc., F.R.S.
H. N. Rydon, D.Sc., D.Phil., F.R.I.C.
N. Sheppard, M.A., Ph.D.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
W. F. Short, D.Sc., M.Sc.
R. Spence, C.B., Ph.D., D.Sc., F.R.I.C.
M. Stacey, Ph.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.
J. Walker, Ph.D., D.Phil., D.Sc.
W. A. Waters, M.A., Sc.D., F.R.I.C.
T. S. Wheeler, Ph.D., D.Sc., F.R.I.C.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, B.A., B.Sc.

FEBRUARY, 1954

Subscription rate to non-Fellows £10 0s. 0d. per annum post free

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1.

THE CHEMICAL SOCIETY

PATRON

HER MAJESTY THE QUEEN

President

C. K. Ingold, D.Sc., F.R.I.C., F.R.S.

Vice-Presidents

who have filled the office of President

F. G. Donnan, C.B.E., D.Sc., LL.D., F.R.S.
Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
W. H. Mills, M.A., Sc.D., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
Sir Robert Robinson, O.M., D.Sc., LL.D., F.R.S.

Vice-Presidents

G. R. Clemo, D.Phil., D.Sc., F.R.S.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
D. H. Hey, Ph.D., D.Sc., F.R.I.C.
E. L. Hirst, D.Sc., LL.D., F.R.S.
Sir John Simonsen, D.Sc., F.R.I.C., F.R.S.
M. Stacey, Ph.D., D.Sc., F.R.S.

Treasurer

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.

Secretaries

H. Burton, Ph.D., D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

Ordinary Members of Council

G. Baddeley, M.Sc., Ph.D., D.Sc.
Wilson Baker, M.A., D.Sc., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
J. Bell, D.Sc., Ph.D., F.R.I.C.
R. P. Bell, M.A., B.Sc., F.R.S.
F. Bergel, D.Phil.Nat., D.Sc., F.R.I.C.
Neil Campbell, D.Sc., Ph.D.
J. Chatt, M.A., Ph.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
I. J. Faulkner, B.Sc., Ph.D., F.R.I.C.
S. J. Gregg, Ph.D., A.R.C.S., F.R.I.C.
Brynmor Jones, Sc.D., Ph.D., F.R.I.C.
F. B. Kipping, M.A., Ph.D.
E. A. Moelwyn-Hughes, D.Phil., D.Sc., Sc.D.
M. W. Perrin, C.B.E., M.A., F.R.I.C.
H. M. Powell, M.A., B.Sc., F.R.S.
A. Robertson, M.A., Ph.D., F.R.S.
M. A. T. Rogers, B.Sc., Ph.D., A.R.I.C.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
J. W. Smith, Ph.D., D.Sc., F.R.I.C.
T. S. Stevens, B.Sc., D.Phil., A.R.I.C.
A. R. J. P. Ubbelohde, M.A., D.Sc., F.R.S.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.

Ex-Officio Member of Council

W. Wardlaw, C.B.E., D.Sc., F.R.I.C. (*Chairman of the Joint Library Committee*)

General Secretary

J. R. Ruck Keene, M.B.E., T.D., B.A.

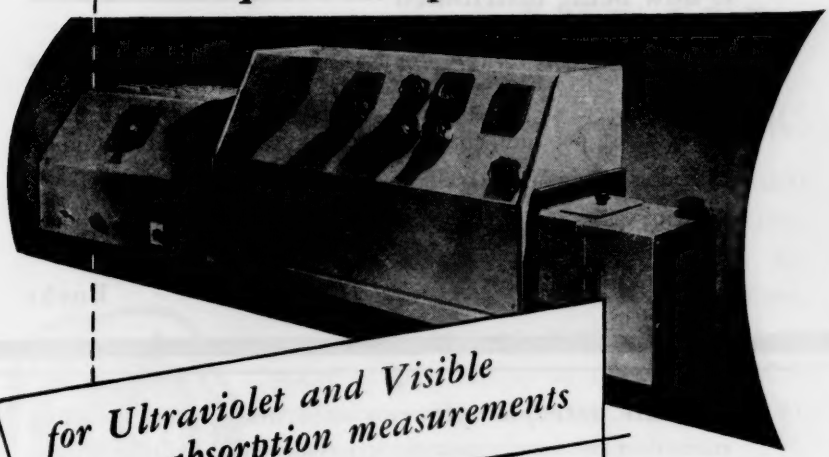
Librarian

A. E. Cummins

Telephone Numbers: Regent 0675/6

SP.500

Spectrophotometer



for Ultraviolet and Visible absorption measurements

The frequency with which the Unicam SP.500 is mentioned in the literature is convincing proof of the sustained quality of its performance and of the wide variety of applications for which it is particularly suitable. For the maintenance of standards of both raw materials and the final product, for academic and medical research, wherever there is a problem of analysis or control, the easiest, most efficient, most economical answer may well be the Unicam SP.500 Spectrophotometer.

UNICAM

An illustrated leaflet describing the instrument in detail will gladly be sent on request.

UNICAM INSTRUMENTS LTD · ARBURY WORKS · CAMBRIDGE

U 1328

LIGHT'S 1954 catalogue

is now being distributed

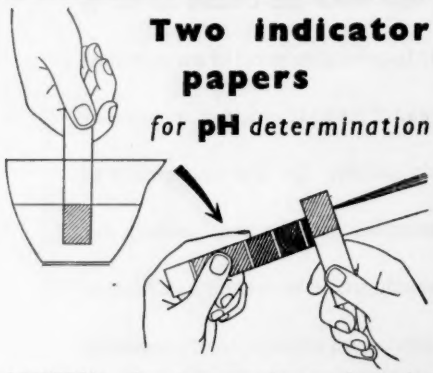
please let us know if you have not received your copy

amino acids, peptides, enzymes, biochemicals, reagents, vitamins, hydrides, pyrimidines, sugars, synthetic drugs, intermediates, solvents, etc.

L. LIGHT & Co. Ltd · Colnbrook · Bucks

Sodium tetraphenylboron—new reagent for Potassium, ammonium and some organic nitrogen compounds—write for *review* to

L. LIGHT & Co. Ltd · Colnbrook · Bucks



Two indicator papers

for **pH** *determination*

UNIVERSAL One paper covering completely the range from 1 to 10 enabling pH values to be checked to within 0.5 pH.

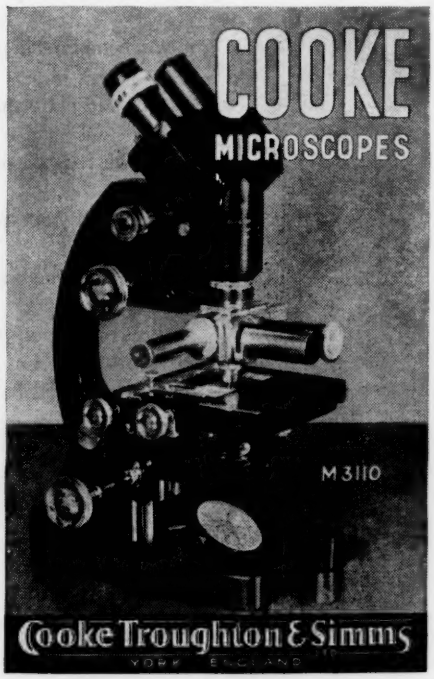
COMPARATOR Four separate books for work requiring greater accuracy. With these papers the pH value of any solution can be ascertained to within 0.3 pH.

Descriptive leaflet will be sent free on request.

JOHNSONS OF HENDON LTD

London, N.W.4

Est. 1743



AT REIGATE [redacted]

OUR JOB

AS ESSENCE MANUFACTURERS

IS TO TAKE NATURAL PRODUCTS WHICH HAVE A FLAVOUR OR AROMA OR BOTH; EXTRACT FROM THEM THE PRINCIPLES RESPONSIBLE FOR THAT FLAVOUR AND AROMA, AND THEN PREPARE THESE PRINCIPLES IN SUCH A FORM AS TO BE EASILY AND CONVENIENTLY AND ECONOMICALLY USED BY OUR CUSTOMERS.

WE ARE SPECIALISTS IN THIS FIELD AND CAN OFFER GUARANTEED NATURAL PRODUCTS WHICH FOR QUALITY AND TRUE FLAVOUR ARE IN A CLASS BY THEMSELVES.

REIGATE BRAND—

VANILLA NATURA
GRAPEFRUIT NATURA
ORANGE NATURA
(SWEET OR BITTER)
ORRIS NATURA

WHITE, TOMKINS & COURAGE, LTD.
NORTH ALBERT WORKS, REIGATE

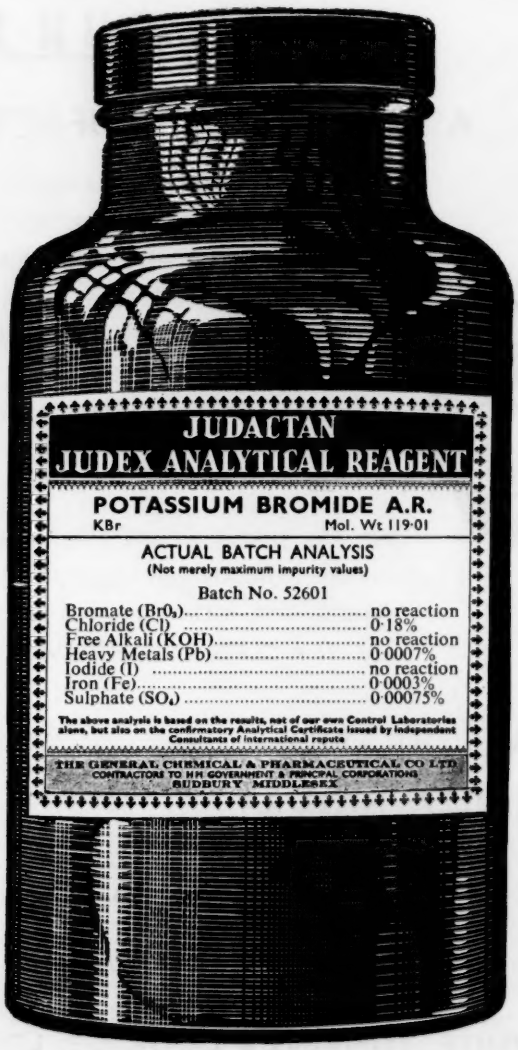
TELEGRAMS: ESSWHITE, REIGATE TELEPHONE: REIGATE 2242–3

ESTABLISHED 1841

JUDACTAN

ANALYTICAL REAGENTS WITH ACTUAL BATCH ANALYSIS

ACTUAL BATCH ANALYSIS


JUDACTAN
JUDEX ANALYTICAL REAGENT
POTASSIUM BROMIDE A.R.
KBr
Mol. Wt 119·01
ACTUAL BATCH ANALYSIS
(Not merely maximum impurity values)
Batch No. 52601
Bromate (BrO3) ..... no reaction
Chloride (Cl) ..... 0·18%
Free Alkali (KOH) ..... no reaction
Heavy Metals (Pb) ..... 0·0007%
Iodide (I) ..... no reaction
Iron (Fe) ..... 0·0003%
Sulphate (SO4) ..... 0·00075%
The above analysis is based on the results, not of our own Control Laboratories alone, but also on the confirmatory Analytical Certificate issued by Independent Consultants of international repute
THE GENERAL CHEMICAL & PHARMACEUTICAL CO LTD
CONTRACTORS TO H.M. GOVERNMENT & PRINCIPAL CORPORATIONS
SUDBURY MIDDLESEX

Each batch subjected to INDEPENDENT ANALYSIS before label is printed

You are invited to compare the above actual batch analysis with the purities guaranteed by the specifications of any competing maker in this country or abroad.

THE GENERAL CHEMICAL & PHARMACEUTICAL CO. LTD.
Chemical Manufacturers, Judex Works, Sudbury, Middlesex

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

The Infra-red Spectra of Some Inorganic Phosphorus Compounds.
By D. E. C. CORBRIDGE and E. J. LOWE 493

The Influence of Uranyl and Thorium Salts on the Miscibility of Phenol and Water.
By S. T. BOWDEN and J. H. PURNELL 535

Miscibility Phenomena in Ternary Systems containing Diphenyl Ether, Water, and an Aliphatic Alcohol or Acid.
By J. H. PURNELL and S. T. BOWDEN 539

The Preparation and Some Properties of Plutonium Fluorides.
By J. K. DAWSON, (MISS) R. M. ELLIOTT, R. HURST, and A. E. TRUSWELL. . . 558

Studies on Bond Type in Certain Cobalt Complexes. Part V. The Exchange Reactions of Cobaltous 1 : 10-Phenanthroline and Tripyridyl Complexes.
By B. O. WEST 578

The Conductivity of Electrolytes in Non-aqueous and Mixed Solvents. Part I.
By V. S. GRIFFITHS 686

Glow-discharge Electrolysis. Part II. The Anodic Oxidation of Ferrous Sulphate.
By A. HICKLING and J. K. LINACRE 711

Electron Transfer in Alkali Metal–Hydrocarbon Complexes.
By W. A. HOLMES-WALKER and A. R. UBBELOHDE 720

Some Surface Properties of Docosyltrimethylammonium Bromide, and of Docosane-1-sulphonic Acid and its Sodium Salt.
By F. G. HOLLIMAN, J. F. LARGIER, and F. SEBBA 738

Adsorption of Ions by Carborundum.
By G. A. H. ELTON and J. W. MITCHELL 741

NOTE :

Tetramethylammonium Amalgam.
By G. B. PORTER 760

Physical Organic.

The Thermal Decomposition of *tert.*-Butylamine.
By H. O. PRITCHARD, R. G. SOWDEN, and A. F. TROTMAN-DICKENSON . . . 546

Conductivity and Solubility Studies of Some Glycollates and Lactates.
By W. P. EVANS and C. B. MONK 550

Electron-transfer Reactions between Metallic Ions, Co-ordination Complexes, and Hæmoglobin.
By PHILIP GEORGE and D. H. IRVINE 587

Kinetics of the Decomposition of Tetralin Hydroperoxide in Acidic and Basic Solvents.
By (MISS) J. E. HAY, (MISS) N. M. JOHNSTONE, C. F. H. TIPPER, and R. K. WILLIAMS 629

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVI. Unimolecular Menschutkin Reactions in Sulphur Dioxide Solution. Remarks on the Theory of Border-line Mechanisms.
By MARJORIE L. BIRD, E. D. HUGHES, and C. K. INGOLD 634

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVII. Halide-ion Exchange with a Simple Alkyl Halide in Sulphur Dioxide Solution.
By C. A. BUNTON, C. H. GREENSTREET, E. D. HUGHES, and C. K. INGOLD . . 642

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVIII. Menschutkin Reactions of Some Simple Alkyl Halides in Sulphur Dioxide Solution.
By C. A. BUNTON, C. H. GREENSTREET, E. D. HUGHES, and C. K. INGOLD . . 647

The Solvolytic Reactions of 2 : 2-Dimethyl-1-phenylpropyl Bromide.
By I. DOSTROVSKY and DAVID SAMUEL 658

Amino-acids and Peptides. Part XI. The Kinetics of the Self-condensation of Glycylglycylglycine Methyl Ester.
By P. S. REES, D. P. TONG, and G. T. YOUNG 662

PAGE

Studies in Spectroscopy. Part VI. Ultra-violet and Infra-red Spectra of Nitrosamines, Nitrites, and Related Compounds.
By R. N. HASZELDINE and J. JANDER 691

Addition of Free Radicals to Unsaturated Systems. Part VI. Free-radical Addition to the Nitroso-group.
By J. JANDER and R. N. HASZELDINE 696

NOTE:

Effect of Solvent on the Optical Rotation of Some Steroid α-Ketols.
By J. K. NORYMBERSKI 762

Organic.

Some Dyes derived from 2-Hydroxymethylbenzothiazole.
By R. A. JEFFREYS 503

Analogues of 8-Hydroxyquinoline having Additional Cyclic Nitrogen Atoms. Part II. Further Preparations, and Some Physico-chemical Properties.
By ADRIEN ALBERT and ALEXANDER HAMPTON 505

Carcinogenic Nitrogen Compounds. Part XVI. Some Condensed Carbazoles and their Thiophen Analogues.
By NG. Ph. BUU-HOÏ and P. JACQUIGNON 513

Michael Condensations with Substituted Sorbic Esters. Part I. Methyl β-*iso*Butenyl-αα′-dimethoxycarbonylglutarate.
By EVANS B. REID and H. WILLIAM SAUSE 516

The Reduction of Some Carbonyl Compounds with Sodium Borohydride.
By EVANS B. REID and JOEL R. SIEGEL 520

Experiments with 5 : 6-Dihydro-4-hydroxy-6-phenyl-2-pyrone. Part II. The Basic Hydrolysis of an α-Bromo- and an αα-Dibromo-β-keto-δ-lactone.
By EVANS B. REID and JOEL R. SIEGEL 525

Tropolones. Part VII. Orientation in Tropolone.
By J. W. COOK, J. D. LOUDON, and D. K. V. STEEL 530

The Chemistry of Plant-growth Regulators. Part I. 2 : 4-Dichloro-6-hydroxyphenoxyacetic Acid and Related Compounds.
By G. W. K. CAVILL and D. L. FORD 565

Some Methyl Derivatives of β-Carboline.
By J. W. COOK, R. M. GAILEY, and J. D. LOUDON 568

Some Quinoline-5 : 8-quinones.
By VLADIMIR PETROW and BENNETT STURGEON 570

Intramolecular Acylation. Part I. The Ring Closure of Some α-Substituted β-1-Naphthylpropionic Acids.
By M. F. ANSELL 575

The Retardation of Benzaldehyde Autoxidation. Part VI. The Actions of a Number of Polycyclic Aromatic Hydrocarbons of Carcinogenic Interest.
By J. R. DUNN, WILLIAM A. WATERS, and (in part) IVAN M. ROITT 580

β-Acetylacrylic (4-Oxopent-2-enoic) Acid in the Diels–Alder Reaction. Part I. Some Derivatives of the Adduct derived from β-Acetylacrylic Acid and Butadiene.
By S. DIXON and L. F. WIGGINS 594

A Spectroscopic Study of the Nature of the Complexes of Purines with Aromatic Compounds.
By J. BOOTH, E. BOYLAND, and S. F. D. ORR 598

The Oxidation of Cellobiose by Periodate.
By FRANK S. H. HEAD and G. HUGHES 603

Alkenylation employing Lithium Alkenyls. Part VIII. Studies on Alkadienyl Derivatives.
By E. A. BRAUDE and E. A. EVANS 607

Meso-ionic Compounds derived from Pyridino(1′ : 2′-1 : 2)glyoxaline.
By N. W. BRISTOW, P. T. CHARLTON, D. A. PEAK, and W. F. SHORT 616

The Preparation of Bis-2-cyanoethyl Derivatives of Aromatic Primary Amines, and their Conversion into 1 : 6-Diketojulolidines. Part III.
By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN 651

PAGE

*iso*Oxazolones. Part VI. The Hydrogenation of 5-Amino*iso*oxazoles. A New Synthesis of Pyrimidines.
By G. Shaw and (Mrs.) G. Sugowdz 665

The Action of Sodium in Liquid Ammonia on Phaeanthine, *OO'*-Dimethylcurine, and *OO'*-Dimethyl*iso*chondrodendrine.
By D. A. A. Kidd and James Walker 669

The Preparation of 4- and 5-*n*-Alkoxy-1-naphthoic and 6- and 7-*n*-Alkoxy-2-naphthoic Acids.
By G. W. Gray and Brynmor Jones 678

Mesomorphism and Chemical Constitution. Part I. The *n*-Alkoxynaphthoic Acids.
By G. W. Gray and Brynmor Jones 683

Epimeric Alcohols of the *cyclo*Hexane Series. Part X. (±)*trans*-3-Methyl*cyclo*hexanecarboxylic Acid and (±)-*trans*-3-Methyl*cyclo*hexylamine.
By F. R. Hewgill, P. R. Jefferies, and A. Killen Macbeth 699

p-Menthane-2 : 3-diols. Part III. Reductions of Diosphenol with Aluminium *iso*Propoxide and with Lithium Aluminium Hydride.
By A. Killen Macbeth and W. G. P. Robertson 701

p-Menthane-2 : 3-diols. Part IV. The Reaction of Mercuric Acetate with (±)-Menthone and (±)-*iso*Menthone.
By P. R. Jefferies, A. Killen Macbeth, and B. Milligan 705

The Relation between Self-condensation and Substitution Processes in the Reactions of *meso*Benzanthrone with Anions.
By William Bradley and F. K. Sutcliffe 708

Studies in the Steroid Group. Part LXIV. Some Reactions starting from 3β-Acetoxy-9α : 11α-epoxyergosta-7 : 22-diene.
By H. B. Henbest and A. A. Wagland 728

Studies in the Steroid Group. Part LXV. Reactions of 11-Hydroxy- and 11-Oxo-5α-steroids.
By A. Crawshaw, H. B. Henbest, and E. R. H. Jones 731

Studies in the Steroid Group. Part LXVI. Formation of Ergost-14-ene-3β : 5α-diol and Related Compounds.
By Peter Bladon 736

Reactions of Methyl α-D-Mannoside with Aldehydes.
By John Honeyman and J. W. W. Morgan 744

Studies in the Synthesis of Cortisone. Part VII. The Preparation of 3β : 17α-Dihydroxy-*allo*pregnane-11 : 20-dione.
By D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker . 747

Wood Saponins. Part I. A Preliminary Investigation of the Saponins from Morabukea [*Mora gonggrijpii* (Kleinh.) Sandwith].
By R. A. Laidlaw 752

Notes :

Observations on the Synthesis of [8-^{13}C]Adenine.
By Maxwell Gordon 757

2-Acetamido-7-methoxyfluorene.
By John H. Weisburger and Elizabeth K. Weisburger 758

2 : 3-Dimethyl-1 : 4-naphthaquinol Bis(dihydrogen Phosphate).
By D. H. Marrian. 760

The Addition of Some Acyl Hypobromites to Allyl Bromide.
By W. G. H. Edwards and R. Hodges 761

The Reaction of Phenyl-lithium with Azobenzene.
By P. F. Holt and B. P. Hughes 764

Obituary Notices :

L. M. Clark 765

William Jacob Jones 765

Sir Thomas Taylor 767

INDEX OF AUTHORS' NAMES.

ALBERT, A., and Hampton, A., 505.
Ansell, M. F., 575.
Barton, D. H. R., Evans, R. M., Hamlet, J. C., Jones, P. G., and Walker, T., 747.
Bird, M. L., Hughes, E. D., and Ingold, C. K., 634.
Bladon, P., 736.
Booth, J., Boyland, E., and Orr, S. F. D., 598.
Bowden, S. T., and Purnell, J. H., 535.
Bowden, S. T. See also Purnell, J. H., 539.
Boyland, E. See Booth, J., 598.
Bradley, W., and Sutcliffe, F. K., 708.
Braude, E. A., and Evans, E. A., 607.
Braunholtz, J. T., and Mann, F. G., 651.
Bristow, N. W., Charlton, P. T., Peak, D. A., and Short, W. F., 616.
Bunton, C. A., Greenstreet, C. H., Hughes, E. D., and Ingold, C. K., 642, 647.
Buu-Hoï, Ng. Ph., and Jacquignon, P., 513.
Cavill, G. W. K., and Ford, D. L., 565.
Charlton, P. T. See Bristow, N. W., 616.
Cook, J. W., Gailey, R. M., and Loudon, J. D., 568.
Cook, J. W., Loudon, J. D., and Steel, D. K. V., 530.
Corbridge, D. E. C., and Lowe, E. J., 493.
Crawshaw, A., Henbest, H. B., and Jones, E. R. H., 731.
Dawson, J. K., Elliott, R. M., Hurst, R., and Truswell, A. E., 558.
Dixon, S., and Wiggins, L. F., 594.
Dostrovsky, I., and Samuel, D., 658.
Dunn, J. R., Waters, W. A., and Roitt, I. M., 580.
Edwards, W. G. H., and Hodges, R., 761.
Elliott, R. M. See Dawson, J. K., 558.
Elton, G. A. H., and Mitchell, J. W., 741.
Evans, E. A. See Braude, E. A., 607.
Evans, R. M. See Barton, D. H. R., 747.
Evans, W. P., and Monk, C. B., 550.
Ford, D. L. See Cavill, G. W. K., 565.
Gailey, R. M. See Cook, J. W., 568.
George, P., and Irvine, D. H., 587.
Gordon, M., 757.
Gray, G. W., and Jones, B., 678, 683.
Greenstreet, C. H. See Bunton, C. A., 642, 647.
Griffiths, V. S., 686.
Hamlet, J. C. See Barton, D. H. R., 747.
Hampton, A. See Albert, A., 505.
Haszeldine, R. N., and Jander, J., 691.
Haszeldine, R. N. See also Jander, J., 696.
Hay, J. E., Johnstone, N. M., Tipper, C. F. H., and Williams, R. K., 629.
Head, F. S. H., and Hughes, G., 603.
Henbest, H. B., and Wagland, A. A., 728.
Henbest, H. B. See Crawshaw, A., 731.
Hewgill, F. R., Jefferies, P. R., and Macbeth, A. K., 699.
Hickling, A., and Linacre, J. K., 711.
Hodges, R. See Edwards, W. G. H., 761.
Holliman, F. G., Largier, J. F., and Sebba, F., 738.
Holmes-Walker, W. A., and Ubbelohde, A. R., 720.
Holt, P. F., and Hughes, B. P., 764.
Honeyman, J., and Morgan, J. W. W., 744.
Hughes, B. P. See Holt, P. F., 764.
Hughes, E. D. See Bird, M. L., 634, and Bunton, C. A., 642, 647.
Hughes, G. See Head, F. S. H., 603.
Hurst, R. See Dawson, J. K., 558.
Ingold, C. K. See Bird, M. L., 634, and Bunton, C. A., 642, 647.
Irvine, D. H. See George, P., 587.
Jacquignon, P. See Buu-Hoï, Ng. Ph., 513.
Jander, J., and Haszeldine, R. N., 696.
Jander, J. See also Haszeldine, R. N., 691.
Jefferies, P. R., Macbeth, A. K., and Milligan, B., 705.
Jefferies, P. R. See also Hewgill, F. R., 699.
Jeffreys, R. A., 503.
Johnstone, N. M. See Hay, J. E., 629.
Jones, B. See Gray, G. W., 678, 683.
Jones, E. R. H., See Crawshaw, A., 731.
Jones, P. G. See Barton, D. H. R., 747.
Kidd, D. A. A., and Walker, J., 669.
Laidlaw, R. A., 752.
Largier, J. F. See Holliman, F. G., 738.
Linacre, J. K. See Hickling, A., 711.
Loudon, J. D. See Cook, J. W., 530, 568.
Lowe, E. J. See Corbridge, D. E. C., 493.
Macbeth, A. K., and Robertson, W. G. P., 701.
Macbeth, A. K. See also Hewgill, F. R., 699, and Jefferies, P. R., 705.
Mann, F. G. See Braunholtz, J. T., 651.
Marrian, D. H., 760.
Milligan, B. See Jefferies, P. R., 705.
Mitchell, J. W. See Elton, G. A. H., 741.
Monk, C. B. See Evans, W. P., 550.
Morgan, J. W. W. See Honeyman, J., 744.
Norymberski, J. K., 762.
Orr, S. F. D. See Booth, J., 598.
Peak, D. A. See Bristow, N. W., 616.
Petrow, V., and Sturgeon, B., 570.
Porter, G. B., 760.
Pritchard, H. O., Sowden, R. G., and Trotman-Dickenson, A. F., 546.
Purnell, J. H., and Bowden, S. T., 539.
Purnell, J. H. See also Bowden, S. T., 535.
Rees, P. S., Tong, D. P., and Young, G. T., 662.
Reid, E. B., and Sause, H. W., 516.
Reid, E. B., and Siegel, J. R., 520, 525.
Robertson, W. G. P. See Macbeth, A. K., 701.
Roitt, I. M. See Dunn, J. R., 580.
Samuel, D. See Dostrovsky, I., 658.
Sause, H. W. See Reid, E. B., 516.
Sebba, F. See Holliman, F. G., 738.
Shaw, G., and Sugowdz, G., 665.
Short, W. F. See Bristow, N. W., 616.
Siegel, J. R. See Reid, E. B., 520, 525.
Sowden, R. G. See Pritchard, H. O., 546.
Steel, D. K. V. See Cook, J. W., 530.
Sturgeon, B. See Petrow, V., 570.
Sugowdz, G. See Shaw, G., 665.
Sutcliffe, F. K. See Bradley, W., 708.
Tipper, C. F. H. See Hay, J. E., 629.
Tong, D. P. See Rees, P. S., 662.
Trotman-Dickenson, A. F. See Pritchard, H. O., 546.
Truswell, A. E. See Dawson, J. K., 558.
Ubbelohde, A. R. See Holmes-Walker, W. A., 720.
Wagland, A. A. See Henbest, H. B., 728.
Walker, J. See Kidd, D. A. A., 669.
Walker, T. See Barton, D. H. R., 747.
Waters, W. A. See Dunn, J. R., 580.
Weisburger, E. K. See Weisburger, J. H., 758.
Weisburger, J. H., and Weisburger, E. K., 758.
West, B. O., 578.
Wiggins, L. F. See Dixon, S., 594.
Williams, R. K. See Hay, J. E., 629.
Young, G. T. See Rees, P. S., 662.

NOTICES TO AUTHORS OF PAPERS

Scientific communications for the *Journal* should be addressed to " The Honorary Secretaries, The Chemical Society, Burlington House, London, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

Communications that have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

Authors are requested to see that their papers conform, as nearly as possible, to the normal conventions of the *Journal*. It is essential that drawings and photographs be presented in the style required by the Society. Every paper must be prefaced by a short summary, but " Notes " do not require a summary. Authors should consult the brochure entitled " The Presentation of Papers for the Journal of the Chemical Society " for detailed instructions and advice on these and cognate matters; Fellows of the Society are entitled to one copy each, gratis, on application to the General Secretary, The Chemical Society, Burlington House, London, W.1; further copies may be obtained at the public price which is 1*s*. 6*d*. each, post free, or 12*s*. 6*d*. per 10 copies, post free.

Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed are reviewed in " Modern Chemical Nomenclature," by Dr. Clarence Smith (*J*., 1936, 1067) (6*d*. post free), and in the Editorial Reports on Nomenclature (*J*., 1950, 3699; 1951, 3515; 1952, 5057) (1*s*. each post free). Much valuable discussion will be found in " British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold and Co., 1948]. Authors should choose their symbols from the " Report by the Symbols Committee of the Royal Society representing the Royal Society, the Chemical Society, the Faraday Society, and the Physical Society, 1951 " (*J*., 1951, 1677) [9*d*. per copy or 12*s*. per 25 copies (post free), obtainable from the General Secretary, The Chemical Society].

Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors.

Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs and the MS. to the Editor.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows paying the Annual Subscription of £4 10*s*. have the following privileges:

To receive a selection of the publications of the Society to a value of £3 0*s*. without further payment.

To purchase additional publications at favourable prices.

To attend all meetings, discussions and lectures of the Society and to introduce two guests.

To consult and borrow books in the Library. Books may be borrowed by post.

To apply for grants from the Research Fund.

To submit papers for publication in the *Journal*.

Fellows under 27 years of age may pay £1 15*s*. per annum and receive:

The *Proceedings*, *Annual Reports on the Progress of Chemistry*, and *Quarterly Reviews* without further payment.

The right to purchase other publications at favourable prices.

All the other privileges of Fellowship.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 50,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London.*—Scientific Meetings of the Society are usually held on two Thursdays in each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London.*—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

A brochure describing the activities of the Society and forms of application for Fellowship can be obtained from THE GENERAL SECRETARY, THE CHEMICAL SOCIETY, BURLINGTON HOUSE, PICCADILLY, LONDON, W.1.

The Infra-red Spectra of Some Inorganic Phosphorus Compounds.

By D. E. C. Corbridge and E. J. Lowe.

[Reprint Order No. 4340.]

The infra-red spectra of 92 salts of phosphorus oxy-acids have been examined in the rock-salt region. Characteristic frequencies are suggested for P–N and P–O–P linkages. Confirmation of a number of frequency assignments made by other workers has been obtained. The absorption frequencies are found to be largely independent of the positive ion, but show considerable variation with the nature of the anion. General absorption bands characteristic of each class of negative ion are listed and their possible use in analysis is indicated. Effects of crystal and molecular structure on the absorption spectra are discussed, and some useful structural information is derived.

Although several papers have recently dealt with the infra-red absorption spectra of organophosphorus compounds, comparatively little attention has been paid to the inorganic derivatives. Miller and Wilkins (*Analyt. Chem.*, 1952, **24**, 1253) record the spectra of a few orthophosphates, but no systematic study of the salts of the other phosphorus oxy-acids appears to have been made. In this work, the spectra of 92 salts have been examined as fine powders in the 5000—650-cm.$^{-1}$ region. These have been investigated with a view to assigning characteristic frequencies to molecular groupings and generally correlating absorption with molecular structure. The use of such spectra in qualitative and quantitative analysis is also discussed.

Experimental.—The compounds examined were mainly products made in these laboratories, though in some instances commercially available materials of "AnalaR" grade were used. Most of the materials had previously been obtained in a high state of purity for other purposes. All spectra were recorded from 5000 to 650 cm.$^{-1}$, a Perkin–Elmer 21C Double Beam Spectrometer being used. The materials were examined as fine powders spread on rock-salt plates. This was accomplished by using a grinding and sedimenting technique similar to that described by Hunt, Bonherd, and Wisham (*ibid.*, 1950, **22**, 1478) although simple grinding sufficed in some cases. Several recent papers (Lecomte, *Analyt. Chim. Acta*, 1948, **2**, 727; Hunt, Bonherd, and Wisham, *loc. cit.*; Keller, Spotts, and Biggs, *Amer. J. Sci.*, 1952, **250**, 453) deal with infra-red absorption of dry powders. The most satisfactory spectra in this case were obtained from powders with particle sizes not greater than about 2·5 μ. A decrease in transmittance above 2000 cm.$^{-1}$ due to scattered radiation was observed in many spectra, but the scattering was not removed on decreasing the maximum particle size to less than 0·5 μ. By taking spectra with Nujol mulls in the high-frequency region, sharper absorptions were obtained in some instances. Specimens were usually about 0·01 mm. thick, thicker samples being used when searching for weak absorptions. Slit widths were 0·038 mm. at 2000 cm.$^{-1}$ and 0·028 mm. at 700 cm.$^{-1}$. Errors in frequency measurement are probably not greater than ±3 wave-numbers in most parts of the spectrum, although with broad peaks and shoulder bands they may be greater.

Results and Discussion

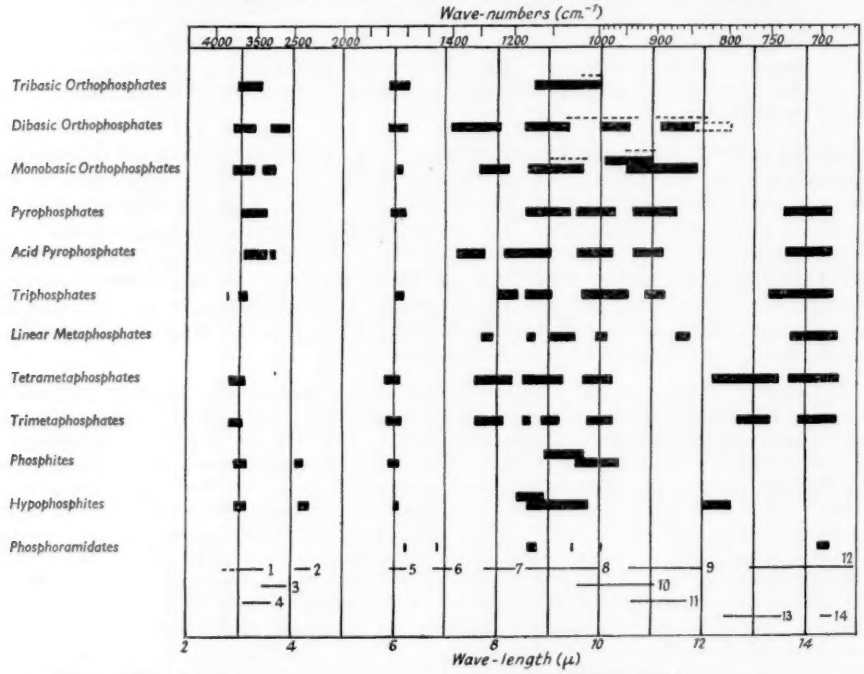
A considerable variation in the quality of the spectra was observed. Some salts, *e.g.*, hypophosphites and cyclic metaphosphates, gave very well-defined spectra, whereas others, particularly some acid orthophosphates, gave broad and poorly resolved peaks. Typical examples are shown in the Figure. The principal absorption bands produced by the various types of anion are summarised in Table 1. These general absorption regions are suggested only inasmuch as the present range of compounds is concerned. Some characteristics of the spectra below 1500 cm.$^{-1}$ are as follows:

Orthophosphates.—The tribasic derivatives give broad absorptions between 1150 and 1000 cm.$^{-1}$, containing only partly resolved peaks in many cases. The absorption generally consists of one very strong broad band between about 1060 and 1000 cm.$^{-1}$, with two or

more weaker bands. The spectra of the acid orthophosphates are more complex. Whilst the strongest peaks usually lie near 1100 cm.$^{-1}$, several additional medium or weak peaks occur in the regions shown in the Table. These bands can be compared with those given by Miller and Wilkins (*loc. cit.*), shown as broken lines.

Pyrophosphates.—The spectra of these compounds are generally better resolved and more consistent than those of the orthophosphates. The strongest absorption, usually consisting of an imperfectly resolved doublet, lies in the region 1170—1060 cm.$^{-1}$. At lower frequencies, bands at 1045—970 cm.$^{-1}$ (two peaks of variable intensity), 940—870 cm.$^{-1}$ (one strong broad absorption and some weaker peaks), and 735—690 cm.$^{-1}$ (one

TABLE 1. *Principal regions of absorption for salts of phosphorus oxy-acids.*

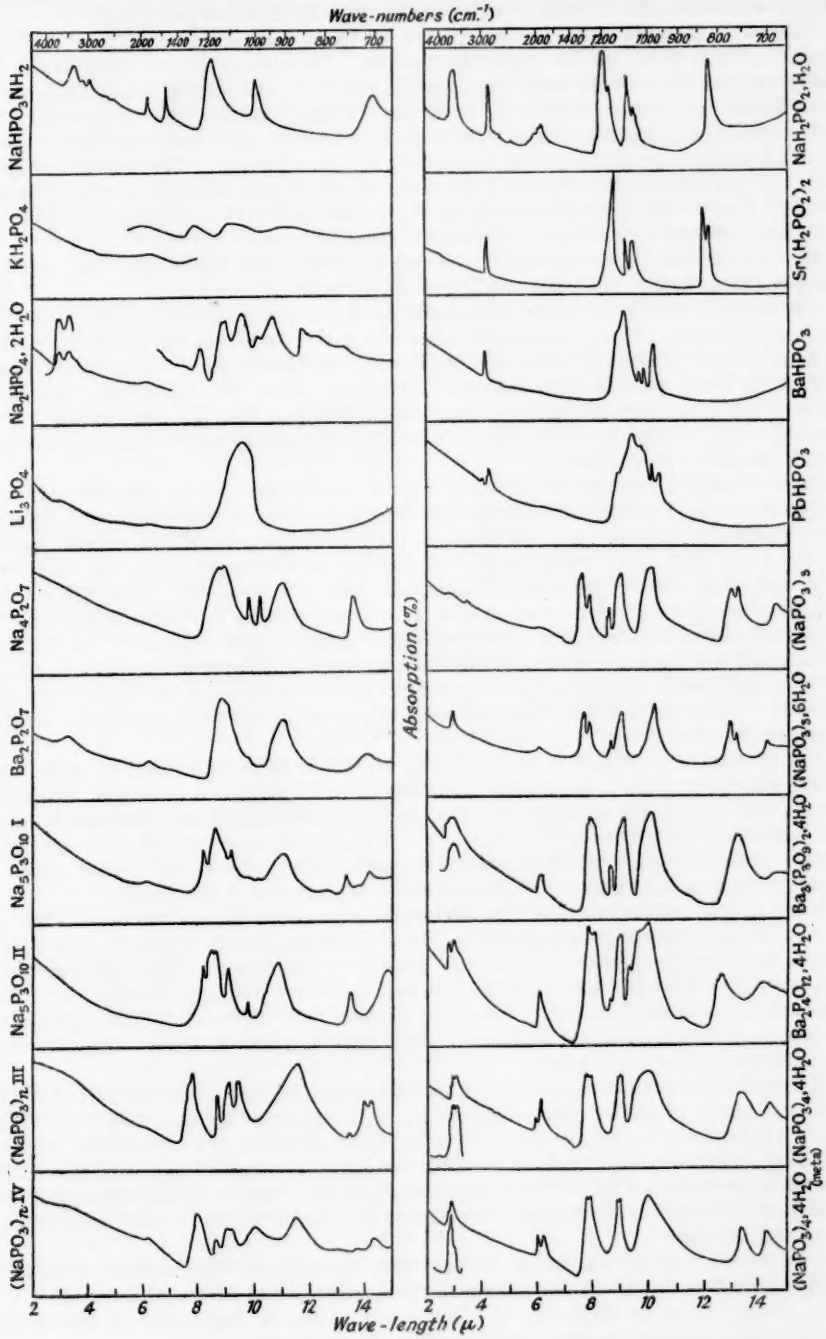


1, O–H stretching in hydrates.
2, P–H stretching.
3, P–O–H stretching.
4, Banded N–H stretching.
5, O–H bending in hydrates.
6, NH_4^+ ion.
7, P=O stretching in triphosphates and metaphosphates.
8, Ionic P–O stretching.
9, P–O–H bending.
10, Other modes of P–O stretching.
11, P–O–P stretching.
12, Harmonics of P–O–P bending.
13, P–O–P in ring systems.
14, P–N stretching.

peak of medium intensity) are usually found. The acid pyrophosphates produce similar absorptions in roughly the same regions with the additional bands shown in the Table.

Triphosphates.—The strongest absorptions in each spectrum are found in the region 1170—1100 cm.$^{-1}$. In addition, a single strong absorption appears in the region 1250—1085 cm.$^{-1}$, and a strong absorption at 920—885 cm.$^{-1}$ in all salts. Two absorptions appear at 1040—955 cm.$^{-1}$ in most cases, and usually two at 755—690 cm.$^{-1}$.

Cyclic Metaphosphates.—The spectra of the metaphosphates are very characteristic, one of the most noteworthy features being the appearance of very strong absorption, usually a triplet, in the 1315—1205-cm.$^{-1}$ region. The very strong broad absorption near 1000 cm.$^{-1}$ is also a distinguishing feature of these compounds. Yet another characteristic is the occurrence of two strong absorptions near 770 cm.$^{-1}$ in addition to medium or weak bands near 700 cm.$^{-1}$. The spectra of a trimetaphosphate and a tetrametaphosphate of a


Wave-numbers (cm.⁻¹)
4000 3000 2000 1400 1200 1000 900 800 700
NaHPO₃NH₂
KH₂PO₄
Na₂HPO₄, 2H₂O
Li₃PO₄
Na₄P₂O₇
Ba₂P₂O₇
Na₅P₃O₁₀ I
Na₅P₃O₁₀ II
(NaPO₃)n III
(NaPO₃)n IV
NaH₂PO₂, H₂O
Sr(H₂PO₂)₂
BaHPO₃
PbHPO₃
(NaPO₃)₃
(NaPO₃)₃, 6H₂O
Ba₃(P₃O₉)₂, 4H₂O
Ba₂P₂O₇, 4H₂O
(NaPO₃)₄, 4H₂O
(NaPO₃)₄, 4H₂O (meta)
Absorption (%)
2 4 6 8 10 12 14
Wave-length (μ)

particular metal are always recognisably different, although the general regions of absorption for these two classes of anion are not greatly different (see Table).

"Linear" Metaphosphates.—The spectra of these compounds exhibit a number of differences from those of the cyclic derivatives. The absorption at 1300—1265 cm.$^{-1}$ usually consists of a single very strong peak, and the very strong broad absorption at 870—850 cm.$^{-1}$ appears to replace the band near 770 cm.$^{-1}$ in the cyclic compounds.

Phosphites and Hypophosphites.—These materials usually give very well-defined spectra, a typical example being strontium hypophosphite (see Figure). The phosphites exhibit several strong absorptions between 1130 and 1035 cm.$^{-1}$ and medium or strong bands at 995—960 cm.$^{-1}$. The hypophosphites on the other hand give absorptions between 1190 and 1025 cm.$^{-1}$ and very strong characteristic absorptions near 820 cm.$^{-1}$.

Phosphoramidates.—Absorptions are found at 1618—1615 and 1470—1468 cm.$^{-1}$, and strong bands at 1162—1143, 994—993, and 697—691 cm.$^{-1}$.

The use of Table 1 for qualitative analysis of phosphate anions, in the form of dry powders, is obvious. Complete identification of a particular metal salt is possible by using the data in Table 2, although failure to match observed bands exactly could result from the same salt's being present in a different crystalline form. No completely satisfactory infra-red technique for quantitative analysis of powders has yet been evolved (Hunt, Bonherd, and Wisham, *loc. cit.*), but the use of the foregoing data in a semi-quantitative manner should be practicable.

Care is needed if spectra are obtained from Nujol mulls. Among the few salts which were also examined in Nujol, some important discrepancies were observed. An absorption found in silver orthophosphate, for instance, may be compared with the values already in the literature: 950 (dry), 965 (Nujol), 970 (Duval and Lecompte, *Bull. Soc. chim.*, 1947, 101), and 947 cm.$^{-1}$ (Bergmann, Littauer, and Pinchas, *J.*, 1952, 847). Silver pyrophosphate gives an absorption at 914 cm.$^{-1}$ in dry powder form and at 880 cm.$^{-1}$ as a Nujol mull, whereas Bergmann, Littauer, and Pinchas report 903 cm.$^{-1}$. A number of differences are found in the spectra of dibasic ammonium phosphate taken as a dry powder and as a Nujol mull, the latter agreeing closely with that recorded by Miller and Wilkins (*loc. cit.*). Differences were found in some other salts but the phenomena were not investigated further.

The spectra of powdered crystalline salts are liable to be influenced by a number of factors, which are usually less important in the case of liquids and solutions. Absorption bands can be broadened, split, or shifted by mutual interaction of adjacent ions or combination with long-wave lattice vibrations. The influence of local crystal structure and the positive ions may also be significant. Moreover, the presence of lattice water and hydrogen bonding may affect the internal modes of vibration of the anions.

Water of Crystallisation.—All the hydrated salts absorb in the 3300 and 1640 cm.$^{-1}$ regions, which presumably correspond to O–H stretching and O–H bending respectively. In most hydrates, frequencies higher than 3450 cm.$^{-1}$ are absent, which indicates that no completely free O–H stretching occurs and that extensive hydrogen bonding is probable. Although a few salts give only a broad absorption near 3300 cm.$^{-1}$, many give several sharp peaks between 3450 and 2860 cm.$^{-1}$ which may be ascribed to more than one type of hydrogen bonding in the crystals.

The hydrated cyclic metaphosphates are exceptional in that a general shift of the O–H stretching bands to higher frequencies occurs, with values as high as 3580 cm.$^{-1}$ in some salts. These absorptions are much sharper and probably correspond to free O–H stretching; moreover, the bands in the O–H bending region are stronger and sharper than in most other hydrated salts. It is apparent, therefore, that in these compounds, some, at least, of the water molecules are only loosely held in the crystal lattice, probably in an interstitial manner.

Another interesting exception is provided by sodium triphosphate hexahydrate $Na_5P_3O_{10},6H_2O$ which gives, in addition to two absorptions at 3350 and 3260 cm.$^{-1}$, a very sharp, strong band at 3630 cm.$^{-1}$. This again indicates that some of the water of crystallisation is probably only loosely held in the structure.

The spectra of the stable and the metastable form of sodium tetrametaphosphate tetra-

hydrate are interesting. The differences between the two crystalline forms (Topley, *Quart. Reviews*, 1949, **3**, 353) appear to be connected with the way some of the water molecules are held in the structure. In both compounds, some water appears to be loosely held (absorption at 3580 cm.$^{-1}$), but the peak at 3330 cm.$^{-1}$ which occurs in the stable form is almost entirely suppressed in the metastable salt. Moreover, in the latter compound the peaks in the O–H bending region are slightly shifted to lower frequencies with a marked reduction of intensity of one of them. The remaining absorptions of the two salts are practically identical.

No correlation was found between any property of the absorptions in the O–H bending and stretching regions, and the number of water molecules in a hydrate. The spectra produced by a hydrate and the corresponding anhydrous salt may be different for two reasons: the introduction of water molecules into the lattice usually results in rearrangement of the packing and the adoption of a different crystalline form, and the water molecules may form hydrogen bonds with some part of the anions and consequently affect their vibrational frequencies.

Comparison of the anhydrous salts with their hydrates reveals a number of differences in their spectra below 1500 cm.$^{-1}$. In many cases a general shift of peaks to lower frequencies occurs. This effect is most marked with peaks in the P–O stretching region (see below) and probably results from hydrogen-bonding of the water molecules on to the oxygen in the anions. A similar phenomenon has been noticed by Bellamy and Beecher (*J.*, 1952, 1701) who observed a shift of the P=O stretching frequency, normally at 1300—1250 cm.$^{-1}$, to considerably lower values in certain organophosphorus acids and amines where hydrogen bonding is very probable. A peculiar effect occurs with sodium hypophosphite. The very strong peak at 817 cm.$^{-1}$ in the monohydrate is split into a triplet in the anhydrous salt. Moreover, the single peak at 2330 cm.$^{-1}$ is also split, into a doublet, on conversion into the anhydrous form.

Polymorphism.—In cases where polymorphism implies merely slightly different packing schemes of similar anions, the differences in infra-red spectra would be expected to be small. On the other hand, when the polymorphism results from differently polymerised anions of the same empirical formula, or from relatively large differences in structural arrangement of similar ions, it is reasonable to expect considerable differences in spectra.

The sodium metaphosphates of general formula $(NaPO_3)_n$ are a case in point. Unfortunately, but few data are available on their internal crystalline structures, but structural differences are indicated by their varied physical properties (Topley, *loc. cit.*, p. 345). *X*-Ray studies of Kurrol salt, $(NaPO_3)_n$-IV (Plieth and Wurster, *Z. anorg. Chem.*, 1951, **267**, 49), show that the crystals contain long chains of linked PO_4 tetrahedra forming anions of high molecular weight. The infra-red spectra of four forms of sodium metaphosphate-II, -III, -IV, and glass * (nomenclature of Partridge, *Chem. Eng. News*, 1949, **27**, 214) are all of the same general type and different from the spectra of the cyclic metaphosphates. This may be an indication that all these compounds are composed of chain-like anions of high molecular weight, as in Kurrol salt. The spectra of forms II and III are almost identical except for one broad absorption which is at 878 cm.$^{-1}$ in the former and at 867 cm.$^{-1}$ in the latter. The somewhat larger divergences, however, among the spectra of the remaining compounds here considered as linear metaphosphates, presumably result from the chains' being polymerised to different extents or from greater differences of crystal structure.

P–O *Linkages.*—In the rock-salt region the PO_4^{3-} ion has two fundamental vibration frequencies, at about 1082 and 980 cm.$^{-1}$. Both these have been observed in Raman spectra, but the latter band, being the ν_1 symmetrical stretching frequency of an XY_4 molecule (Herzberg, "Infra Red and Raman Spectra of Polyatomic Molecules," New York, 1945, p. 167), should not normally appear in infra-red absorption. Colthup (*J. Opt. Soc. Amer.*, 1950, **40**, 397) records for phosphate ions a band at 1100—1040 cm.$^{-1}$ only. Bellamy and Beecher (*loc. cit.*), Miller and Wilkins (*loc. cit.*), and others have also observed absorption in this region.

* Glass obtained by melting NaH_2PO_4 at 700—725° for ½ hr., then chilling it by pouring it on to a stainless-steel plate.

TABLE 2. *Positions and intensities of infra-red absorption bands.*

Orthophosphates

(1) Li_3PO_4

~1100 vs
1050 vs
1035 vs

(2) Na_3PO_4

1125 s to 1028 vs, b
914 vw

(3) $Mg_3(PO_4)_2$

1140 s
1110 s, sh
1068 vs
~1030 m

(4) $Ca_3(PO_4)_2$

1093 vs, sh	1070 vs, sh
	1045 vs

(5) $Sr_3(PO_4)_2$

~1140 m, sh	1068 vs
	1040 vs
	1015 vs

(6) $Ba_3(PO_4)_2$

1090 w, sh	1043 s
1125 m	1000 vs

(7) $Pb_3(PO_4)_2$

1056 vs 981 vs, b

(8) Ag_3PO_4

1037 s 950 vs, b

(9) $CrPO_4,6H_2O$

2915 vs, b	1010 vs, vb
1610 m, b	

(10) $FePO_4,2H_2O$

3330 s, b	1105 vs
1600 s, b	1068 vs
1385 m?	1005 vs
1255 vw?	850 m?

(11) $FeNH_4PO_4,H_2O$

3400 m	1430 m
3210 m	1105 ms
2915 m	1047 s
2760 m	~960 w
1633 w, b	941 w
1470 m	

(12) $MgNH_4PO_4,6H_2O$

3400 m	1105 m
3255 m	1062 s
1700 w	1024 s
1682 w	990 s
1475 m	953 w
1436 m	890 w
1236 m?	767 w
1168 m	

(13) $NH_4H_2PO_4$

3200 s, b	1444 s
3040 m, b	1406 s
2860 w, b	1275 s
~2700 w, b	1084 vs, b
~1640 m, b	900 m, vb

(14) NaH_2PO_4

~2750 m, b	1045 s
1650 m	981 s, b
1300 m	927 s, b
1282 m	870 m
1160 s	815 vw
1125 s	

(15) KH_2PO_4

1285 s, vb	890 s, vb
1085 s, vb	

(16) $Ca(H_2PO_4)_2$

2850 w, b	990 w
1643 vw, b	935 w
~1300 vw	877 w
1128 s, vb	
1072 m	

(17) $Ca(H_2PO_4)_2,H_2O$

3425	1150 w
3180	1090 s, b
2910	~980 s, sh
1650 m	963 vs
1240 m	913 w
1220 m, sh	890 w

(18) $NaH_2PO_4,2H_2O$

3500	1100 s
3420	1040 s
3250 b	~990 w, sh
2700 w, b	958 s
1658 m	903 s
1280 m, sh	888 w, sh
1245 m	820 vw
1163 s	

(19) $(NH_4)_2HPO_4$

3350 s	1450 w
3225 s	1409 m
3125 s	1240 w
3025 s	1070 vs, b
~2700 vw, b	996 s
~1650 vw	951 w
1486 m	884 m
1468 m	

(20) Na_2HPO_4

2750 w, b	1065 s, b
1240 w	991 s
1350 w	973 m
1310 w	940 b
1148 s	~850 s, b
1125 s	798 m
1100 s	

(21) K_2HPO_4

2900 m	996 s
2550 w	983 s
1650 w, b	952 m
1328 w	847 s, b
1110 vs, b	800 w?

(22) $CaHPO_4$

~2800 w	1130 s
~1620 w, vb	1068 s
1390 w	993 w
1350 w	890 w, b
1170 m, sh	

(23) $Na_2HPO_4,2H_2O$

3450 s	1133 s
3360 s	1120 s
3080 s	1067 s
2700 w, b	990 m
1700 w, b	950 s
1257 m	862 m
	815 w

Pyrophosphates

(24) $Li_4P_2O_7,2H_2O$

~3350 m	940 vs
2860 vw	896 m
~1640 m	738 w
1195 m	
1170 vs	
1150 vs	
1128 vs	
1107 vs	

(25) $Na_4P_2O_7$

1180 s, sh	988 s
1165 s, sh	921 vs, b
1150 vs	895 m
1124 vs	735 vs
1031 s	

(26) $K_4P_2O_7$

1110 vs	980 w
1080 s, sh	930 m
1050 s, sh	890 vs, b
1025 s	720 m

(27) $Na_4P_2O_7,10H_2O$

3420 s	1021 w
3230 s	993 m
3000 s	921 s, b
1655 m	865 m
1110 vs	665 m, vb
1093 vs	

(28) $Mg_2P_2O_7$

1161 vs	932 m
1122 vs	907 m
1049 m	725 m
1008 w	

(29) $Ca_2P_2O_7$

1153 vs	1000 w
to 1080 m	927 m, b
1035 w	720 w

(30) $Sr_2P_2O_7$

1142 vs	1030 m
1125 vs	981 w
1108 m, sh	888 s
1091 m, sh	722 m
1072 m	

(31) $Ba_2P_2O_7$

1135 vs	977 w
1110 vs	912 s, b
1021 w	718 m

32) $Pb_2P_2O_7$

1117 vs	972 m
1061 vs	914 s
1003 m	728 m

(33) $(NH_4)_4P_2O_7$

1460 s	868 vs, b
1405 s	737 vw
1164	702 w
1105 vs	
~1070	
~1045	

(34) $Ag_4P_2O_7$

1093 vs	972 w
1063 vs	914 s, b
1046 vs	701 m
998 m	

(35) $Na_2H_2P_2O_7$

~2700 w, b	1155 s
1600 m, vb	1027 w
1389 w	957 m
1333 w	878 s, b
1210 m	729 m
1191 s, sh	

(36) $(NH_4)_2H_2P_2O_7,xH_2O$

3275 w	1175 m, sh
3150 w	1153 s
3000 m	1118 s
~2800 vw	1045 s, b
~2600 vw	986 s
1465 m	935 s, b
1415 m	692 m
1292 m	

(37) $CaH_2P_2O_7$

~2700 vw	970 s
1280 vs	895 s, b
1212 m	830 vw, b
1094 s	735 m

Triphosphates

(38) $Na_5P_3O_{10}$-I

~1620 w, vb	989 w
1265 w	912 s, b
1215 s	798 vw, b
1146 vs	753 m
1095 s	731 w
1022 w	708 s

(39) $Na_5P_3O_{10}$-II

1214 s	1016 w
1184 s	906 vs, b
1165 vs	737 m
1145 vs	665 s
1098 s	

(40) $Na_5P_3O_{10},6H_2O$

3630 s, sh	1118 s
3350 m	1100 s
3260 m	1080 s
1651 w	959 w
1610 w	887 vs, b
1410 w	768 w, b
1211 s	710 m
1157 s	

(41) $K_5P_3O_{10}$

1208 s	874 vs, vb
1156 s	726 m
1130 vs, b	683 m
1090 s	

TABLE 2. (*Continued.*)

(42) $Ag_5P_3O_{10}$

1306 vw	999 m
1170 m, sh	970 m
1097 s	893 s, b
1082 s	760 vw, b
1067 s	716 m
1047 s	701 s

(43) $Zn_2NaP_3O_{10},9H_2O$

3470 m	1044 m
3330 s, b	1026 m
1664 m	997 s
1625 m	916 vs, b
1243 s	781 m
1150 vs	710 w
1107 vs	

(44) $NiNa_3P_3O_{10},12H_2O$

~3175 s, vb	1088 s
1642 w	1025 m
1249 s	992 m
1141 s	913 m, b
1119 s	750 w, vb

Trimetaphosphates

(45) $Na_3P_3O_9$

1314 s, sh	1101
1298 vs	987 vs, b
1262 s	773 vs
1169 s	757 vs
1162 s	686 s
1120 s, sh	

(46) $Na_3P_3O_9,H_2O$

3465 m	1112 s
1680 w, b	1100 s
1610 w, b	970 vs, b
~1315 m	774 s
1292 vs	755 s
1260 vs	695 m
1158 m	

(47) $Na_3P_3O_9,6H_2O$

3485 s	1100 s
~1640 w, b	975 vs, b
1312 m	776 s
1294 vs	756 s
1270 s	698 m
1159 m	

(48) $Mg_3(P_3O_9)_2,10H_2O$

3480 s	1170 vw
3280 s, b	1100 vs
1680 s	1023 vs, vb
1642 s	977 m
1317 s	~900 vw
1271 vs	784 vs
1250 vs	690 vw, b

(49) $CaNaP_3O_9,3H_2O$

3580 w	1116 s
1655 m	1012 s, b
1625 s	900 vw
1320 m	772 vs
1303 vs	767 s
1275 vs	~700 w
1168 m	

(50) $Sr_3(P_3O_9)_2,7H_2O$

3560 m	1157 s
3510 m	1108 vs
3330 s, b	996 vs, b
1645 m	788 m
1620 m	765 s
1295 vs	697 m
1275 vs	
1256 vs	

(51) $Ba_3(P_3O_9)_2,4H_2O$

3560 m	1113 s
3340 s, b	1097 vs
1640 s	1085 vs
1612 s	1012 vs
1298 vs	983 vs
1265 vs	757 vs, b
1245 vs	685 m
1153 m	

(52) $Mn_3(P_3O_9)_2,11H_2O$

~3500 m	1170 w
3120 vs, b	1097 vs
1665 m	1012 vs, vb
1640 s	780 vs
1280 s	720 vw, b
1265 s	685 w, b
1235 vs	

(53) $Ag_3P_3O_9$

~1315 m	1132 m
1277 s	1106 s
1242 s	1085 s
1210 m	1068 s
1156 m	

Tetrametaphosphates

(54) $Na_4P_4O_{12}$

1306 s	1037 vs, b
1282 s	to 991 vs, b
1270 s	882 vw, b
1173 vw	794 m
1125 vs	710 m
1093 m	

(55) $Na_4P_4O_{12},4H_2O$

3580 w	1109 vs
3480 m	998 vs, vb
3330 m	880 vw?
1693 w	748 m
1655 m	697 m
1290 vs	
1266 vs	
1122 vs	

(56) $Na_4P_4O_{12},4H_2O$ (metastable)

3580 w	1109 vs
3475 m	988 vs, vb
3330 vvw	880 vw?
1670 w	750 m
1622 w	697 m
1284 vs	
1265 vs	
1117 vs, sh	

(57) $Ag_4P_4O_{12},2H_2O$

3415 w, vb	1087 s
1630 w, b	991 vs
1400 w, I?	978 vs
1360 w, I?	958 s
1250 s	797 m
1232 s	714 m
1206 s	693 m

(58) $Mg_2P_4O_{12},8H_2O$

~3600 s	1157 vs
3400 vs	1115 s
3330 vs	1030 vs, b
1665 s	797 m
1650 s	748 s
1315 vs	718 s
1253 vs	

(59) $Ca_2P_4O_{12},5H_2O$

3560 m	1120 s
3420 m	1108 m, sh
2980 w	~1030 vs, b
1655 w	1010 vs, b
1625 m	888 vw?
1290 vs, b	800 m
1260 vs, b	732 m, b
1148 s	691 w

(60) $Sr_2P_4O_{12},5H_2O$

3630 s	1238 m
3580 vs	1153 vw
3380 vs	1125 m
1645 vs	1110 vs
1625 vs	1008 vs, vb
1285	755 s
1277 vs	720 m
1258 s	

(61) $Ba_2P_4O_{12},4H_2O$

3570 vs, sh	1108 vs
3400 vs	1073 s
3180 m	1030 vs
1645 s	1000 vs
1281 vs	987 vs
1258 vs	885 vw?
1240 vs	798 s
1154 w	788 s
1120 vs	706 m

(62) $Pb_2P_4O_{12},4H_2O$

~3300 w	1147 w
1665 w	1095 s
1620 w	995 vs, b
1278 m	816 m
1260 vs	748 m
1235 vs	720 m, b

(63) $Mn_2P_4O_{12},9H_2O$

3400 vs, vb	1106 s
1625 s	1025 vs, vb
1290 vs	785 w
1238 vs	740 s
1140 vs	708 s

(64) $Cu_2P_4O_{12},8H_2O$

3550 s	1154 s
3400 vs	1105 s
3230 vs	1024 vs, vb
1645 s	910 vw
1298 vs	750 s
1250 vs	717 m

(65) $Al_4(P_4O_{12})_3$

1311 vs	1066 vs
1286 s	1029 vs
1230 w	808 m
1183 m	738 s
1143 m	718 m
1083 s	

Metaphosphates of high molecular weight

(66) $(NaPO_3)_n$-II

~1315 m, sh	1060 s
1298 vs	878 vs, vb
1160 m	742 w
1104 s	719 m
1097 s	702 m

(67) $(NaPO_3)_n$-III

~1315 m, sh	1060
1298 vs	867 vs, vb
1160 m	742 w
1104 s	719 m
1097 s	702 m

(68) $(NaPO_3)_n$-IV

~1630 w, b	996 s, b
1268 vs, vb	869 vs, b
1150 m	778 w
1110 s	724 w
to 1082 s	698 m

(69) $(NaPO_3)_n$(glass)

1262 vs, b	863 m
1150 w	770 vw, vb
1083 s, b	to 700 vw, vb
980 m, vb	

(70) $(KPO_3)_n$

1300 s	1015 w, b
1266 vs	851 vs, b
1150 s	760 m
1100 s, b	677 s

Orthophosphites

(71) Li_2HPO_3,H_2O

3450 s	1117 vs
3400 m	1096 vs
3250 m	1080 vs
2380 m	1045 w
2360 m	1038 w
1640 m	1005 w
1173 s	994 s

(72) Na_2HPO_3

2300 m, b	1037 w
1116 vs, b	993 m
to 1082 vs, b	972 w

(73) $Na_2HPO_3,5H_2O$

3225 vs, vb	1082 s, b
2320 w	1037 vs, b
1670 m	972 m

(74) $CaHPO_3,H_2O$

3360 m	1130 s, b
3300 m	1054 s, b
2430 m	1018 w
1665 m	996 s

TABLE 2. (*Continued.*)

(75) $SrHPO_3,H_2O$

3230 s, b	1068 vs
2382 m	1057 vs, sh
2340 m	1011 w
1680 w	993 s
1124 s	

(76) $BaHPO_3$

2400 m	1022 m
1130 s, sh	1006 m
1082 vs, b	978 s

(77) $PbHPO_3$

2373 w	1058 s
2340 m	1028 s
1126 s, sh	1012 m
1075 s	988 s
	963 s

(78) $NiHPO_3,H_2O$

3325 vs, vb	1088 vs
2400 w	1060 vs
2355 w	1020 s, sh
1640 m	995 s, sh
1120 s	

Hypophosphites

(79) LiH_2PO_2

2325 s	1100 s
1180 vs	1073 s
1148 s	817 vs

(80) NaH_2PO_2

2350 s	1092 s
2280 s	1080 vs
1966 vw	1065 s
1634 vw	1053 m
1190 vs	830 vs
1171 s	817 vs
1150 m	800 vs
1100 m	

(81) NaH_2PO_2,H_2O

3270 vs, vb	1098 w
2330 vs	1088 vs
1964 vw	1071 s
~1690 w	1060 w
1640 m	1045 w
1185 vs	817 vs
1167 s	

(82) KH_2PO_2

3400 m, b	1097 w
2295 s	1080 s
1964 vw	1065 s
1220 m	1050 s
1208 m	820 s
1195 s	810 s
1185 vs	800 s
1162 s	

(83) $Mg(H_2PO_2)_2,6H_2O$

3460 m	1110 s
3200 s, b	1075 m
2400 s	1020 m
2350 w	808 m
1665 m	760 m, vb
1153 m	

(84) $Ca(H_2PO_2)_2$

2360 s	1092 m
1184 vs	1063 m
1170 s	1042 m
1148 s	813 vs
1100 s	

(85) $Sr(H_2PO_2)_2$

2360 s	1054 s
1150 vs	834 vs
1082 s	824 s

(86) $Ba(H_2PO_2)_2$

2350 s	1078 s
1965 w	1040 s, b
~1170 s	822 vs
1147 s	811 vs
1090 s	

(87) $Pb(H_2PO_2)_2$

2355 s	1073 s
1950 w	1046 s
1191 m	1029 s
1128 vs, b	817 vs
1105 m	806 vs

(88) $Mn(H_2PO_2)_2$

2340 m	1093 w
1665 w, b	1081 m
1188 vs	1060 m
1160 vs	1051 m
1148 s	1043 m
1122 w	1033 m

Phosphoramidates

(89) $NaH(PO_3{\cdot}NH_2)$

2875 s, b	1615 m
2580 w	1158 vs, b
2470 w	994 s
2045 w	697 s

(90) $KH(PO_3{\cdot}NH_2)$

2890 m, b	1469 m
2585 w	1162 s
2475 w	993 m
2055 vw	691 m
1618 m	

(91) $NH_4H(PO_3{\cdot}NH_2)$

3260 m	1470 m, sh
3130 m	1457 m
2760 s, b	1415 s
2585 w	1143 vs, b
2445 w	994 m
2160 w	898 vw, b
1616 w	694 m

(92) $Ag_2(PO_3{\cdot}NH_2)$

2960 m, vb	1060 vs
1612 w, b	1011 m
1183 m	978 s
1154 m	952 m
1128 s	907 w
1100 s	824 w
1083 s	782 m, b

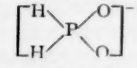
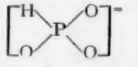
Amongst the tribasic orthophosphates, we have found strong absorptions between 1150 and 1000 cm.$^{-1}$ which we attribute to the ionic phosphate vibration. However, in all compounds which we have studied, strong absorptions, often consisting of multiplet peaks, occur over the range 1170—1000 cm.$^{-1}$, and these also are presumably connected with some kind of P–O ionic stretching. Although the ranges in which absorption occurs shown in Table 1 appear to be shifted to higher frequencies in some cases, no correlation could be found between the position of the absorption in each salt and the type of anion.

The P–O–P *Linkage.*—Our results show that compounds containing P–O–P links produce characteristic absorptions near 900 and near 700 cm.$^{-1}$. Limited studies with organophosphorus compounds have attributed bands near 700 cm.$^{-1}$ to P–O–P stretching (Holmstedt and Larson, *Acta Chem. Scand.*, 1951, **5**, 179) and bands at 950—930 cm.$^{-1}$ to P–O–P links (Bergmann, Littauer, and Pinchas, *loc. cit.*). The P–O–P stretching bands near 900 cm.$^{-1}$ appear to shift towards lower frequencies with increasing length of the P–O–P chain, in the pyrophosphate, triphosphate, and linear metaphosphate series of salts. The absorption near 700 cm.$^{-1}$, which also appears to be connected with P–O–P linkages, usually consists of two peaks in the triphosphates and metaphosphates, but only one peak in the case of pyrophosphates which contain a single P–O–P linkage. The cyclic metaphosphates show absorption near 700 cm.$^{-1}$ and also near 770 cm.$^{-1}$, the latter band replacing the one nearer 900 cm.$^{-1}$ in the chain compounds. The lower vibrational frequencies in the cyclic derivatives may be characteristic of P–O–P linkages in such ring systems.

The P–O–P stretching region at 940—850 cm.$^{-1}$ can be compared with Si–O–Si stretching at 1050—1025 cm.$^{-1}$ (Richards and Thompson, *J.*, 1949, 124) and P–O–$C_{Aliphatic}$ at 1070—1010 cm.$^{-1}$ (Bellamy and Beecher, *loc. cit.*). Wright and Hunter (*J. Amer. Chem. Soc.*, 1947, **69**, 803) attribute very strong absorption near 400 cm.$^{-1}$ to Si–O bending in Si–O–Si chains and suggest harmonics of this vibration near 800 cm.$^{-1}$ in several methyl-

siloxanes. The bands observed near 700 cm.$^{-1}$ in the phosphates containing P–O–P linkages may likewise be due to harmonics of P–O bending.

P–H *Linkage.*—Previous studies with phosphine (Herzberg, *op. cit.*, p. 164) and with organophosphorus compounds (Bellamy and Beecher, *J.*, 1952, 475; Daasch and Smith, *Analyt. Chem.*, 1951, **23**, 883) have established a band at 2400—2300 cm.$^{-1}$ as due to P–H stretching. Our findings support this contention, absorptions being found at 2430—2300 cm.$^{-1}$ in phosphites and 2400—2280 cm.$^{-1}$ in hypophosphites. Moreover, when comparable specimens of a phosphite and a hypophosphite were used, the latter was invariably found to give a much stronger peak. This is to be expected if there are two P–H linkages in one instance and only one in the others, and is compatible with the formulæ (I) and (II) for the hypophosphite and phosphite ions respectively.

(I)   (II)

The P–H bending frequency is to be expected in the region 1150—950 cm.$^{-1}$, but it was not observed by Daasch and Smith (*loc. cit.*), who concluded that the absorption was probably very weak. The inorganic phosphites and hypophosphites give absorptions in this region, but these may be due to other causes which are discussed below.

P–O–H *Stretching.*—Characteristic of the acid orthophosphates and acid pyrophosphates is a weak, broad absorption near 2700 cm.$^{-1}$. Absorption in this region has been assigned to P–OH stretching (Daasch and Smith, *loc. cit.*; Bellamy and Beecher, *loc. cit.*).

P–N *Stretching.*—A strong absorption appears near 700 cm.$^{-1}$ in each of the phosphoramidates. Our attribution of this to P–N stretching is supported by the following calculation: For a simple harmonic oscillator,

$$\nu = 1307\sqrt{k/\mu} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ν is the frequency in cm.$^{-1}$, μ is the reduced mass of the two atoms concerned, and k is the force constant $\times$ 10^{-5} in dynes/cm. From Gordy's relation (*J. Chem. Phys.*, 1946, **14**, 305) for the force constant, *viz.*,

$$k = 1{\cdot}67N\left(\frac{x_A x_B}{d^2}\right)^{\frac{1}{4}} + 0{\cdot}30 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k is the force constant $\times$ 10^{-5} dynes/cm., N is the bond order, x_A,x_B are the electronegativities (P = 2·1, N = 3·0), d is the internuclear distance, P–N = 1·785 Å (Hobbs, Corbridge, and Raistrick, *Acta Cryst.*, 1953, **6**, 621), this gives a value of k = 3·08 $\times$ 10^{-5} dynes/cm., which, substituted in equation (1), gives a value of $\nu_{calc.}$ = 738 cm.$^{-1}$. If the three hydrogen atoms (see below) are included in the expression for the reduced mass, $\nu_{calc.}$ = 692 cm.$^{-1}$, whereas the experimental value in sodium phosphoramidate is $\nu_{obs.}$ = 697 cm.$^{-1}$.

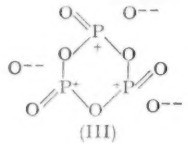
The monobasic phosphoramidates all exhibit absorption at 1618—1615 and 1470—1468 cm.$^{-1}$, which may be ascribed to zwitterion formation in this type of compound (cf. amino-acids). The existence of the phosphoramidate anion in the zwitterion form in the crystalline structure has recently been demonstrated (Hobbs, Corbridge, and Raistrick, *loc. cit.*).

Ammonium Salts.—All the ammonium salts give two absorptions near 1400 cm.$^{-1}$, which can be ascribed to the NH_4^+ ion. Absorptions due to bonded N–H stretching appear around 3000 cm.$^{-1}$ in the phosphoramidates and in most ammonium salts.

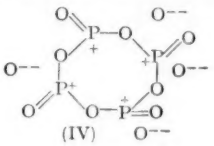
1050—850-cm.$^{-1}$ *Region.*—The assignment of P–O–P stretching at 940—850 cm.$^{-1}$ has already been discussed. Other absorptions in this region can be connected with several causes. The ν_1 symmetrical stretching frequency of the PO_4^{3-} ion might appear in special circumstances. The strong band at 950 cm.$^{-1}$ in silver orthophosphate is probably due to Ag–O covalent bond formation, as pointed out by Bergmann, Littauer, and Pinchas (*loc. cit.*). Distortion of the PO_4 tetrahedron in the silver salt has been inferred from bond-length measurements (Pauling, "The Nature of the Chemical Bond," Cornell University Press, New York, 1944, p. 243). A distorting effect might ensure from the presence of a heavy polarisable cation, as, *e.g.*, in lead orthophosphate, where a strong absorption is recorded at 981 cm.$^{-1}$.

A number of absorptions are found at 1050—850 cm.$^{-1}$ in the acid orthophosphates and acid pyrophosphates. Some of these are probably connected with the P–OH deformation frequency (Bellamy and Beecher, *loc. cit.*), while others may be due to modification of the symmetry of the PO_4 tetrahedra by the attached hydrogen atoms. Bands at about 1030 and 980 cm.$^{-1}$ in trialkyl phosphates have been attributed to antisymmetrical and symmetrical stretching, respectively, of the three P–OR groups (Bergmann, Littauer, and Pinchas, *loc. cit.*). Similar symmetrical stretching of the P–O linkages in the phosphite and phosphoramidate ions may account for the absorption observed in the 980-cm.$^{-1}$ region in these compounds.

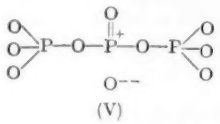
Miscellaneous Bands.—The strong peaks observed in the 1100-cm.$^{-1}$ region in the metaphosphates have already been associated with ionic P–O stretching; the bands near 1000 cm.$^{-1}$ may also result from a stretching mode of the ionic phosphate groupings. The very strong bands in the 1300—1200 cm.$^{-1}$ region are not, however, easily explained. This region is normally assigned to P=O stretching and the P–O links outside the rings may be presumed to be of the same nature. The great strength of the absorption suggests a substantial ionic contribution in this linkage. Bond-length measurements on the crystal structure of ammonium tetrametaphosphate (Romers, Ketelaar, and MacGillavry, *Acta Cryst.*, 1951, **4**, 119) reveal significant shortening of the P–O bonds external to the ring. Structures such as (III), (IV), and (V) may make a significant contribution to the resonating state of these anions, thus accounting for both the short bonds and the strong absorption.



(III)



(IV)



(V)

The bands at about 1400—1220 cm.$^{-1}$, generally of medium intensity, in the acid phosphates may be due to a combination of the P–O stretching frequency with a lattice band, as suggested by Oberly and Weiner (*J. Chem. Phys.*, 1952, **20**, 740).

The very strong peaks near 820 cm.$^{-1}$ in the hypophosphites may be connected with torsional oscillations or rocking motions of the ion, since it is unlikely they are connected with P–H bending or P–O bending.

Effect of Positive Ions.—The influence of the cations on the spectra do not appear to be very marked, except in the case of the silver salts. In all silver salts, a pronounced shift of some peaks to lower frequencies is observed. This is particularly evident with those absorptions in the ionic P–O stretching region, as, *e.g.*, with the orthophosphate, pyrophosphate, and triphosphate salts. These shifts are probably bound up with the tendency for formation of silver–oxygen covalent bonds (see p. 501). Shift of peaks to lower frequencies in the case of some lead salts occurs, but is of a less marked extent.

With the remaining salts, a tendency for the shift of certain peaks to lower frequencies with increasing mass of the cation is noticeable in a few cases, but no systematic correlation between frequency and any property of the positive ion could be found. This progressive shift is most evident with the group of strong peaks in the ionic P–O stretching region, with the Mg, Ca, Sr, Ba, and Pb salts of the tribasic orthophosphates and pyrophosphates.

This work is being extended to other phosphorus compounds, and measurements will be made in the potassium bromide region. A more detailed correlation of absorption with molecular structure may be possible with the aid of Raman and polarised infra-red techniques. Particular interest lies in the crystalline and glassy metaphosphates, where infra-red absorption studies may throw some light on their constitution.

We thank Mr. J. E. Such and other members of the staff for providing some of the compounds used in the investigation.

RESEARCH DEPARTMENT, ALBRIGHT & WILSON LTD.,
OLDBURY, BIRMINGHAM.

[*Received, May 26th*, 1953.]

Some Dyes derived from 2-Hydroxymethylbenzothiazole.

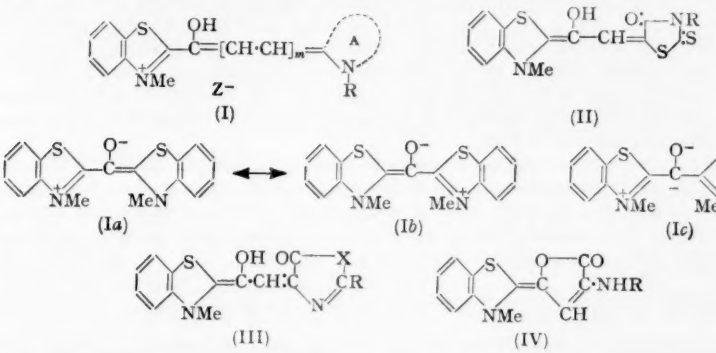
By R. A. JEFFREYS.

[Reprint Order No. 4641.]

Preparations defined in the title are described.

ZUBAROVSKI (*J. Gen. Chem., U.S.S.R.*, 1951, **21**, 2055) has described a number of derivatives of hydroxymethylbenzothiazole, including the quaternary salt ethiodide. He stated, however, that owing to certain difficulties he was unable to isolate cyanine dyes with a hydroxyl substituent in the polymethin chain. This paper describes the preparation and properties of several of these dyes.

When 2-hydroxymethyl-3-methyl- and 3-methyl-2-methylthio-benzothiazolium toluene-*p*-sulphonate were refluxed together in ethanol with 1 mol. of triethylamine, an orange dye crystallized, whose empirical formula corresponded to (I; A = benzothiazoline, $m = 0$, R = Me, Z = $C_6H_4Me{\cdot}SO_3$). The solution in aqueous ethanol was cerise, in pyridine purple, and in ethanol with a drop of triethylamine it was blue. All of these solutions slowly faded and became colourless. It is probable that the deep colour in basic solutions was due to the degenerate zwitterionic resonance system (I*a*) ⟷ (I*b*), wherein any structure such as (I*c*) is prohibited by the adjacent negative charges.



(I) (II) (I*a*) (I*b*) (I*c*) (III) (IV)

A trimethincyanine was prepared from the hydroxymethyl quaternary salt and 2-2′-acetanilidovinyl-3-ethylbenzoxazolium iodide with 1 mol. of base. This dye (I; A = benzoxazoline, $m = 1$, R = Et) was orange-red ($\lambda_{max.}$ 520 mμ) in ethanol, and addition of a drop of triethylamine produced a transient green colour.

Two *mero*cyanine dyes (II; R = $CH_2{\cdot}CH{:}CH_2$ and R = $CH_2{\cdot}CO_2Et$) possessing a thiazolid-4-one ring were prepared from the appropriate 5-ethoxymethylene intermediates. These dyes were magenta ($\lambda_{max.}$ 560 mμ) in ethanol, and basification produced a transient blue colour, quickly fading to colourless. The dyes were easily acetylated to the *mero*-cyanines with an acetoxy-group on the chain, which had absorption maxima similar to dyes with unsubstituted chains.

A common property of all of these dyes is their rapid decomposition in basic solutions, although before completely decomposing they exhibit the deep colours pertaining to dyes with O^- in the chain.

When the 2-hydroxymethyl quaternary salt and 4-ethoxymethylene-2-ethylthiothiazol-5-one were condensed in the presence of a base the initial colour of the solution was magenta. However, this colour quickly became degraded and only a yellow dye having $\lambda_{max.}$ 470 mμ was isolated. The analogous dye from 4-ethoxymethylene-2-phenyloxazol-5-one was also yellow ($\lambda_{max.}$ 467 mμ), and neither of these dyes was affected by alkali, although their analyses were similar to those for the hydroxy-dyes. By analogy with the structures of the thiazolid-4-one *mero*cyanines it may be deduced that the initial dyes formed were

(III; X = S, R = SEt) and (III; X = O, R = COPh), the former being responsible for the observed magenta colour. It is also known that the thiazolone and oxazolone rings present in these dyes are easily opened at the $C_{(5)}$–S and $C_{(5)}$–O bonds (Cook *et al.*, *J.*, 1948, 1056, 1060) providing carboxylic acids, esters, and amides. These intermediates formed from (III) are γ-hydroxy-ketones, which may cyclize to the lactones (IV; R = CS_2Et, COPh). The latter structures account for the properties including the similar absorption spectra, of these dyes.

Experimental

2-Hydroxymethyl-3-methylbenzothiazolium toluene-*p*-sulphonate was prepared from 2-hydroxymethylbenzothiazole (Zubarovski, *loc. cit.*) (1·65 g.) and methyl toluene-*p*-sulphonate (1·86 g.) on the steam-bath during ¼ hr. The product solidified.

Bis-(3-methyl-2-benzothiazole)hydroxymethincyanine Toluene-p-sulphonate.—2-Hydroxymethyl-3-methylbenzothiazolium toluene-*p*-sulphonate (3·51 g.) and 3-methyl-2-methylthiobenzothiazolium toluene-*p*-sulphonate (3·67 g.) with triethylamine (1·4 c.c.) in ethanol (10 c.c.) were heated for 10 min. on the steam-bath. The *dye* was filtered off and recrystallized from methanol–ether as orange needles (2·5 g.), m. p. 200° (Found: N, 5·6; S, 19·3. $C_{24}H_{22}O_4N_2S_3$ requires N, 5·6; S, 19·4%). It had $\lambda_{max.}$ in MeOH at 490 mμ, and addition of triethylamine produced a blue solution, $\lambda_{max.}$ 596 mμ.

[3-(3-*Ethyl*-2-*benzoxazole*)][1-*hydroxy*-1-(3-*methyl*-2-*benzothiazole*)] *trimethincyanine Perchlorate.*—2-Hydroxymethyl-3-methylbenzothiazolium toluene-*p*-sulphonate (3·51 g.) and 2-2′-acetanilidovinyl-3-ethyl benzoxazolium iodide (4·34 g.) with triethylamine (1·4 c.c.) in ethanol (15 c.c.) were refluxed for ½ hr. The cooled solution was poured into aqueous sodium perchlorate. An oil formed which slowly solidified. It recrystallized from pyridine–ethanol–ether as maroon leaflets, m. p. 208° (decomp.) (Found: H, 5·3; N, 5·8; S, 6·6. $C_{29}H_{19}O_6N_2ClS$,EtOH requires H, 5·0; N, 5·6; S, 6·5%). The orange-red solution in ethanol, which had $\lambda_{max.}$ at 520 mμ, slowly changed to green with a drop of triethylamine, its absorption maxima becoming 462 mμ and 583 mμ.

3-*Allyl*-5-[2-*hydroxy*-2-(3-*methylbenzothiazolin*-2-*ylidene*)*ethylidene*]-2-*thiothiazolid*-4-*one.*—2-Hydroxymethyl-3-methylbenzothiazolium toluene-*p*-sulphonate (3·51 g.) and 3-allyl-5-ethoxymethylene-2-thiothiazolid-4-one (2·27 g.) with triethylamine (1·4 c.c.) in ethanol (15 c.c.) were refluxed for 5 min. The *dye* was filtered off and recrystallized from pyridine–methanol as a dark green powder (3·7 g.), m. p. 184° (Found: H, 4·2; N, 7·6; S, 26·7. $C_{16}H_{14}O_2N_2S_3$ requires H, 3·9; N, 7·7; S, 26·5%). An ethanol solution of the dye was magenta and had $\lambda_{max.}$ at 560 mμ. Addition of a drop of triethylamine to the solution produced an evanescent turquoise colour.

3-*Ethoxycarbonylmethyl*-5-[2-*hydroxy*-2-(3-*methylbenzothiazolin*-2′-*ylidene*)*ethylidene*]-2-*thiothiazolid*-4-*one.*—This *dye* was prepared similarly, by using 3-ethoxycarbonylmethyl-5-ethoxymethylene-2-thiothiazolid-4-one (2·75 g.). It recrystallized from pyridine–methanol as purple leaflets (3·4 g.) which darkened from 176 to 190°, with indeterminate melting or decomp. point (Found: N, 6·9; S, 23·7. $C_{17}H_{16}O_4N_2S_3$ requires N, 6·9; S, 23·5%). The magenta solution in ethanol had $\lambda_{max.}$ 560 mμ and changed to blue on addition of triethylamine.

In a similar preparation, involving 4-ethoxymethylene-2-ethylthiothiazol-5-one (2·17 g.) at room temperature, a magenta colour developed, but soon became degraded, and only a yellow *dye*, possibly (IV; R = CS_2Et), was isolated. It recrystallized from pyridine–methanol as buff needles (1·8 g.), m. p. 172° (decomp.) (Found: N, 7·9; S, 27·6%). It had $\lambda_{max.}$ 470 mμ in MeOH, and was stable to acid and alkali.

A similar *dye*, possibly (IV; R = COPh), was obtained from the reaction between the hydroxymethyl quaternary salt and 4-ethoxymethylene-2-phenyloxazol-5-one (2·17 g.) with triethylamine in ethanol. It recrystallized from nitrobenzene–ethanol as orange leaflets (1·0 g.), m. p. 289°, $\lambda_{max.}$ 467 mμ in MeOH (Found: N, 8·0; S, 9·2%).

5-[2-*Acetoxy*-2-(3-*methylbenzothiazolin*-2-*ylidene*)*ethylidene*]-3-*allyl*-2-*thiothiazolid*-4-*one.*—3-Allyl-5-[2-hydroxy-2-(3-methylbenzothiazolin-2-ylidene)-ethylidene]-2-thiothiazolid-4-one (0·5 g.) in acetic anhydride (10 c.c.) was refluxed for 10 min. The initial blue colour faded to magenta in a few minutes. The solution was cooled and poured into water (50 c.c.). The *dye* was filtered off and recrystallized from benzene–light petroleum as blue prisms, m. p. 187° (Found: N, 6·8; S, 23·9. $C_{18}H_{16}O_3N_2S_3$ requires N, 6·9; S, 23·8%). In ethanol the dye had $\lambda_{max.}$ 530 mμ, and on addition of a drop of alkali the solution became blue, and then colourless.

5-[2-*Acetoxy*-2-(3-*methylbenzothiazolin*-2-*ylidene*)-*ethylidene*]-3-*ethoxycarbonylmethyl*-2-*thiothi-*

azolid-4-one.—In the same way 3-ethoxycarbonylmethyl-5-[2-hydroxy-2-(3-methylbenzothiazoline-2-ylidene)-ethylidene]-2-thiothiazolid-4-one was acetylated. The *product* recrystallized from benzene–light petroleum as magenta needles, m. p. 164°, $\lambda_{max.}$ 532 mμ in EtOH (Found: N, 6·4; S, 21·3. $C_{19}H_{18}O_5N_2S_3$ requires N, 6·2; S, 21·3%).

RESEARCH LABORATORIES, KODAK LTD.,
WEALDSTONE, HARROW, MIDDLESEX.

[*Received, September 8th*, 1953.]

Analogues of 8-Hydroxyquinoline having Additional Cyclic Nitrogen Atoms. Part II. Further Preparations, and Some Physico-chemical Properties.*

By ADRIEN ALBERT and ALEXANDER HAMPTON.

[Reprint Order No. 4662.]

Syntheses are described of 8-hydroxy-4-methyl-, 8-hydroxy-4-propyl- and 7-allyl-8-hydroxy-quinazoline. It is shown that acetic formic anhydride can formylate primary aromatic amines quantitatively at 5°.

Ionization constants and oil–water partition coefficients of thirteen analogues of 8-hydroxyquinoline have been determined and correlated with structure. The stability constants of the ferric, ferrous, cupric, and nickel complexes of these analogues are reported. The relative basic strength of the two nitrogen atoms in each of the following has been determined: 8-hydroxyquinazoline, 5-hydroxyquinoxaline, 4-hydroxy-1:5-naphthyridine, 8-hydroxy-1:6-naphthyridine, and 8-hydroxy-1:7-naphthyridine.

The acidic ionization constants of the monohydroxypyridines are reported and used in a discussion of the variations in acidic strength of nitrogenous heteroaromatic substances.

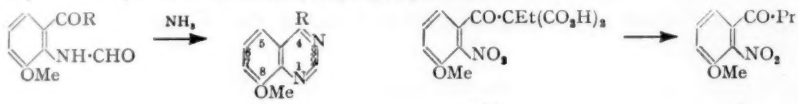
IT is known that the outstanding antibacterial properties of 8-hydroxyquinoline (oxine) are due, not to oxine itself, but to the 1:1 complex which it forms with traces of iron in the medium (Albert, Gibson, and Rubbo, *Brit. J. Exp. Path.*, 1953, **34**, 119). Preliminary investigation of the analogues described in Part I* showed that the introduction of ring-nitrogen atoms had lowered the oil–water partition coefficient and, in proportion as this fell, the antibacterial action sharply decreased. In the expectation of restoring antibacterial action by raising the partition coefficient, small alkyl groups were inserted into the molecules of 8-hydroxycinnoline and 8-hydroxyquinazoline. This expectation was realized, supporting the hypothesis that the site of action of oxine is intracellular (Albert, Hampton, Selbie, and Simon, *Brit. J. Exp. Path.*, in the press). The present study reports the preparation of the alkyl-hydroxyquinazolines, also the determination of physical properties which shed light on the mode of action (particularly partition coefficients and the stability constants of the metal complexes).

8-Hydroxy-4-methylquinazoline was prepared by modifications of Bischler's general method (*Ber.*, 1891, **24**, 506; 1893, **26**, 1350) for the synthesis of quinazolines (*e.g.*, I⟶II). Attempts to prepare 2-formamido-3-methoxyacetophenone (I; R = CH_3) by heating 2-amino-3-methoxyacetophenone with formic acid under various conditions destroyed much of the amine. However, quantitative formylation occurred when the amine was shaken at 5° with acetic formic anhydride (cf. du Vigneaud and Meyer, *J. Biol. Chem.*, 1932, **98**, 295). Passing ammonia into a solution of (I; R = CH_3) in molten ammonium acetate (according to a general method of Schofield, Swain, and Theobald, *J.*, 1952, 1924) readily gave 8-methoxy-4-methylquinazoline (II; R = CH_3). Aluminium chloride converted this into 8-hydroxy-4-methylquinazoline.

3-Methoxy-2-nitrophenyl propyl ketone (IV), required for the synthesis of 8-hydroxy-4-propylquinazoline, was conveniently prepared by Bowman's method for the synthesis of ketones (*J.*, 1950, 325). Condensation of 3-methoxy-2-nitrobenzoyl chloride with dibenzyl sodioethylmalonate, followed by hydrogenolysis, gave the malonic acid (III), which

* Part I, *J.*, 1952, 4985.

yielded the desired ketone (IV) on being warmed. Reduction of (IV) with iron–acetic acid gave 2-amino-3-methoxyphenyl propyl ketone which was smoothly converted into the 2-formamido-ketone (I; R = Pr^n) with acetic formic anhydride. 8-Methoxy-4-propylquinazoline (II; R = Pr) was obtained (50% yield) therefrom by use of ammonia in molten ammonium acetate or, better, by the normal Bischler synthesis. Demethylation with aluminium chloride gave 8-hydroxy-4-propylquinazoline. Application of the general method of Brown and Murphy (*J. Amer. Chem. Soc.*, 1951, **73**, 3308) (treatment of the sodio-derivative of 8-methoxy-4-methylquinazoline in liquid ammonia with ethyl iodide) gave only a small yield of 8-methoxy-4-propylquinazoline.



(I) (II) (III) (IV)

8-Allyloxyquinazoline (prepared from 8-hydroxyquinazoline and allyl bromide) gave 7-allyl-8-hydroxyquinazoline by Claisen rearrangement.

TABLE 1. *Physical properties of analogues of 8-hydroxyquinoline.*

No.	Compound	Solubility (H_2O at 20°; M)	pK_a (in H_2O) * Basic pK_a	M	Acidic pK_a	M	Partition coeff. (20°): oleyl alcohol–H_2O, pH 7·3
1	8-Hydroxyquinoline	0·0039	5·13 (± 0·02)	0·004	9·89 (± 0·03)	0·004	67
2	8-Hydroxycinnoline	0·0039	2·74 (± 0·02) [a]	0·005	8·20 (± 0·04)	0·003	5·6
3	8-Hydroxyquinazoline	0·0092	3·41 (± 0·01)	0·01	8·65 (± 0·02)	0·005	5·2
4	5-Hydroxyquinoxaline	0·045	0·9 (± 0·1) [a]	0·01	8·65 (± 0·04)	0·01	7·8
5	4-Hydroxy-1 : 5-naphthyridine	0·0057	2·85 (± 0·02)	0·01	10·01 (± 0·05)	0·005	<0·02
6	8-Hydroxy-1 : 6-naphthyridine	0·022	4·08 (± 0·02)	0·01	8·33 (± 0·02)	0·005	1·00
7	8-Hydroxy-1 : 7-naphthyridine	0·072	2·64 (± 0·04)	0·10	12·01 (± 0·05)	0·01	0·14
8	4-Hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX)	0·0086	<2	0·01	8·95 (± 0·02)	0·009	<0·02
9	2′-Hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII)	0·065	<1·3	0·05	11·05 (± 0·05)	0·01	<0·02
10	4′-Hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII)	0·028	<1·3	0·05	8·78 (± 0·03)	0·01	<0·02
11	8-Hydroxy-4-methylcinnoline	0·0021	3·18 (± 0·02)	0·005	8·34 (± 0·05)	0·002	16·3
12	8-Hydroxy-4-methylquinazoline	0·0025	2·90 (± 0·01)	0·005	8·75 (± 0·05)	0·002	16·5
13	8-Hydroxy-4-propylquinazoline	0·0012	[e]	—	8·82 (± 0·04)	0·001	135
14	7-Allyl-8-hydroxyquinazoline	0·00024	[c]	—	[c]	—	310
15	Cinnoline	—	2·70 [b]	0·007	—	—	—
16	Quinazoline	—	3·51 [b]	0·07	—	—	—
17	4-Methoxycinnoline	—	3·21 (± 0·08)	0·033	—	—	—
18	4-Methoxyquinazoline	—	3·13 (± 0·05)	0·033	—	—	—
19	4-Hydroxypteridine (VI)	0·03 [d]	<1·5 [d]	—	7·89 [d]	—	<0·02

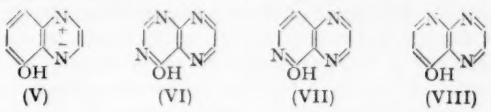
* pK_a = negative logarithm of the ionization constant.
[a] This, and similar low pK_a values, were determined by back-titration of an otherwise supersaturated solution. [b] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [c] Too insol. for accurate measurement (see text). [d] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [e] Confirmed spectrometrically.

Ionization Constants.—These were determined potentiometrically as an essential preliminary to obtaining the stability constants of the metallic complexes. Table 1 shows that the introduction of one additional cyclic nitrogen atom into 8-hydroxyquinoline is invariably base-weakening. This effect, which varies in intensity with position and tends to be intensified if more than one nitrogen is introduced, is attributed to the electron-attracting property of the entering nitrogen atom (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240). The positions where an extra ring-nitrogen atom is most base-weakening are 2-, 4-, 5-, and 7-. In these positions the resonance of the molecule can be strengthened, at the expense of the resonance of the ion, by dipolar structures involving two nitrogen

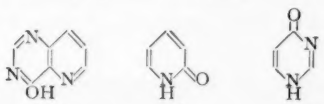
atoms, *e.g.*, (V) and its counterpart with the charges reversed (Table 1, Nos, 2, 4, 5, and 7). Considerations of valency debar this type of resonance when the second nitrogen is in the 3- or the 6-position (Nos. 3 and 6). The basic pK_a of 5-hydroxyquinoxaline, previously given as 2·15 (Freeman and Spoerri, *J. Org. Chem.*, 1951, **16**, 438), is now found to be 0·9 which agrees with a figure obtained spectrophotometrically (Irving and Rossotti, personal communication).

The basic pK_a of 8-hydroxy-4-methylcinnoline is almost 0·5 unit higher than that of 8-hydroxycinnoline, in accordance with the usual slight base-strengthening effect of methyl groups in heterocyclic compounds (Albert, Goldacre, and Phillips, *loc. cit.*). Nevertheless, 8-hydroxy-4-methylquinazoline is a weaker base than 8-hydroxyquinazoline. A similar contrast exists between 4-methoxy-cinnoline and -quinazoline (Table 1): the former is 0·5 pK_a unit stronger than cinnoline; but the latter is 0·4 unit weaker than quinazoline.

As expected, the nitrogenous analogues of 8-hydroxyquinoline are stronger acids than the parent substance. Exceptions are those analogues with a nitrogen atom replacing $C_{(7)}$, *viz.*, 8-hydroxy-1 : 7-naphthyridine and 2′-hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII). A nitrogen atom replacing $C_{(5)}$ is also slightly acid-weakening, as may be seen by comparing 4-hydroxy-1 : 5-naphthyridine with 8-hydroxyquinoline, and 4′-hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII) with 5-hydroxyquinoxaline. However, when nitrogen



(V) (VI) (VII) (VIII)



(IX) (X) (XI)

atoms are introduced at both $C_{(5)}$ and $C_{(7)}$ in 8-hydroxyquinoline an increase in acidic strength results. Thus 4-hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX) is stronger by 0·9 pK unit than 8-hydroxyquinoline, while 4-hydroxypteridine (VI) is 0·8 unit stronger than 5-hydroxyquinoxaline. These effects on the hydroxyl group, obviously connected with its attachment sometimes to an aromatic, sometimes to a heteroaromatic, ring, were clarified by determination of the pK values of the monohydroxypyridines, as tabulated.

Acidic pK_a *of hydroxypyridines and related compounds* (20°).

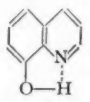
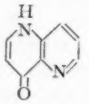
Compound	Phenol	2-Hydroxy-pyridine	3-Hydroxy-pyridine	4-Hydroxy-pyridine	2-Hydroxy-pyrimidine	4-Hydroxy-pyrimidine
Acidic pK_a (in H_2O at 20°)	9·98 [a]	11·62 (± 0·03)	8·72 (± 0·02)	11·09 (± 0·04)	9·17 [b]	8·59 [b]
Concn. at which determined	M/50	M/100	M/100	M/100	M/100	M/30

[a] Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058.
[b] Albert, Brown, and Cheeseman, *loc. cit.* 5-Hydroxypyrimidine is unknown.

The weak acidic strength of 2- and 4-hydroxypyridine relative to that of phenol is connected with the tendency of the un-ionized molecule to exist as a cyclic amide (X), or a vinylogue thereof. 3-Hydroxypyridine, which cannot form a cyclic amide, is not only more acidic than its isomers, but even more acidic than phenol because its nitrogen atom is electron attracting. 2- and 4-Hydroxypyrimidine can exist as cyclic amides, *e.g.*, (XI), but only one of the nitrogen atoms is involved whereas the other exerts an acid-strengthening effect. Hence they are stronger acids than either 2- or 4-hydroxypyridine. The variations in acidic pK_a among the analogues of 8-hydroxyquinoline can be explained similarly.

Oil–Water Partition Coefficients.—It has been shown that the distribution of a series of substances between water and various poorly miscible liquids always follows the same order, although the less water-soluble liquids give the greater spread of values (Collander, *Acta physiol. Scand.*, 1947, **13**, 363). Oleyl alcohol was used in preference to vegetable oils in the present studies because it is less viscous and more readily purified; in addition it is

representative of the fatty alcohols found in cytoplasmic membranes. Reference to Table 1 shows that, as expected, all the nitrogenous analogues of 8-hydroxyquinoline are considerably less lipophilic than the parent substance. Of the analogues with only one extra nitrogen atom, 4-hydroxy-1 : 5-naphthyridine and 8-hydroxy-1 : 7-naphthyridine have especially low partition coefficients. This is interpreted as follows: in aqueous solution at pH 7, 8-hydroxyquinoline is internally hydrogen-bonded, as (XII). Thus it has only one principal centre of hydration (the oxygen atom), whereas the above two naphthyridines, which are almost certainly cyclic amides, *e.g.*, (XIII), would possess three centres of hydration and hence be very much less lipophilic than 8-hydroxyquinoline. 4-Hydroxyquinoline, which is similar in structure to 4-hydroxy-1 : 5-naphthyridine (XIII), has been found to

(XII)   (XIII)

have an enol : amide ratio of 1 : 10,000 (Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923). The infra-red spectra (as solids) of the other analogues having two nitrogen atoms showed no bands characteristic of carbonyl group absorption (Dr. L. N. Short, personal communication). The three analogues having three nitrogen atoms (Nos. 8—10) all have partition coefficients below the limit of measurement by our method (<0·02).

The insertion of small alkyl groups adjacent to one or other of the two centres of hydration (the oxygen atom and $N_{(3)}$) in 8-hydroxyquinazoline greatly increased the partition coefficient. The increase was 3-fold with a methyl group at $C_{(4)}$, 26-fold with a *n*-propyl group at $C_{(4)}$, and 60-fold with an allyl group at $C_{(7)}$. Nos. 2 and 11 show a similar relationship.

TABLE 2. *Stability constants of the metal complexes of analogues of 8-hydroxyquinoline (in* H_2O *at* 20°).

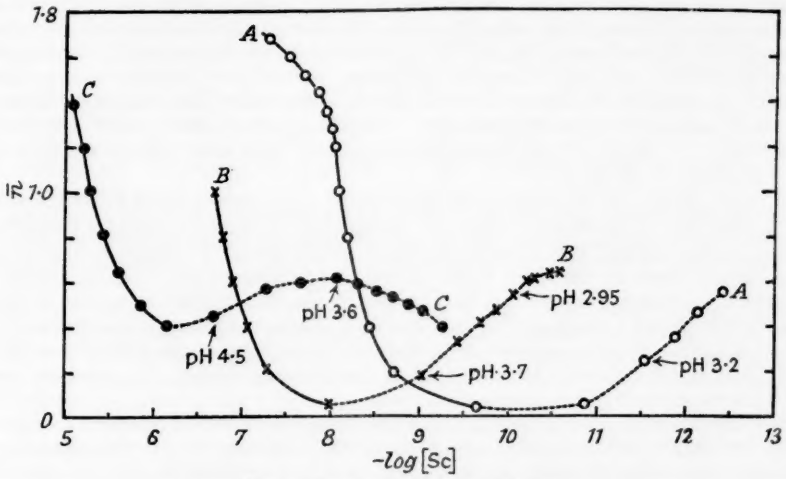
No.	Compound	Fe^{3+} complex log K'[b]	Fe^{3+} complex log K_s[d]	Cu complex log K'	Cu complex log K_s[h]	Ni complex log K'	Ni complex log K_s[h]	Fe^{2+} complex log K'	Fe^{2+} complex log K_s[h]
1	8-Hydroxyquinoline[a]	12·3	—	12·2	—	9·9	—	8·0	—
1*a*	8-Hydroxyquinoline-5-sulphonic acid[a]	12·0	33	12·5	23·1	10·0	18·1	8·4	15·1
2	8-Hydroxycinnoline	9·6	[e]	9·1	[e]	7·8[f]	14·9	6·7	[e]
11	8-Hydroxy-4-methylcinnoline	—	—	—	—	8·1	[e]	—	—
3	8-Hydroxyquinazoline	10·6	27·7	9·3	[e]	7·6[f]	14·4	6·6	12·2
12	8-Hydroxy-4-methylquinazoline	—	—	—	—	7·9	14·7	—	—
4	5-Hydroxyquinoxaline	9·3	25·8	[e]	[e]	7·6	[e]	6·8	[e]
5	4-Hydroxy-1 : 5-naphthyridine	11·0	27·8	6·9	13·4	5·8	10·5	5·8[f]	10·7
6	8-Hydroxy-1 : 6-naphthyridine	10·3	25·9		14·2	5·9[f]	10·9	5·9	10·5
7	8-Hydroxy-1 : 7-naphthyridine	12·2	[e]	8·3[f]	16·2	6·7	12·4	6·2	11·7
8	4-Hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX)	—	—	—	—	6·1[f]	11·5	—	—
9	2′-Hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII)	11·0	[e]	7·5[f]	14·7	6·1[f]	11·3	5·4[f]	9·9
10	4′-Hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII)	—	—	—	—	5·9[f]	11·0	—	—
19	4-Hydroxypteridine[a] (VI)	[e]	[e]	4·8[f]	9·5	4·4	7·8	3·4[f]	5·9

[a] Values taken from Albert, *Biochem. J.*, 1953, **54**, 646. [b] K' (the stability constant of the complex formed by addition of only one ligand molecule to one metallic cation) is given by $K' = \bar{n}/(1 - \bar{n})[Sc]$, where [Sc] is the concentration of the free chelating species (ligand anions) and $\bar{n}$ is the average number of molecules of ligand bound by one atom of metal. [c] No combination appeared to take place. [d] K_s (the overall stability constant) = $K' . K'' . K'''$. [e] Complex is too insol. for measurement. [f] Approx. value, the difference between log K' and log K'' being less than 1 unit (cf. Albert, *loc. cit.*). [g] Evaluation impossible, owing to simultaneous chelation by the zwitterionic species. [h] Calc. from $K_s = 1/[Sc]^3$ at $\bar{n} = 1$.

Stability Constants of Metal Complexes.—Some stability constants of the complexes of the analogues of 8-hydroxyquinoline with ferric, ferrous, cupric, and nickel ions are listed

in Table 2, together with the known constants for 8-hydroxyquinoline and 8-hydroxyquinoline-5-sulphonic acid (Albert, *Biochem. J.*, 1953, **54**, 646). (The K' values of this acid are almost identical with those for 8-hydroxyquinoline and hence it is likely that the K_s values of both substances are very close. Unfortunately the insolubility of the 1 : 2 complexes of 8-hydroxyquinoline interferes with measurement of K_s.)

It is seen from Table 2 that the analogues having one additional nitrogen atom, especially the hydroxynaphthyridines, have less avidity for metallic ions than 8-hydroxyquinoline has; this difference is most evident for the bivalent ions. The analogues with two additional nitrogen atoms have approximately the same chelating ability as the hydroxynaphthyridines, but chelate more readily than 4-hydroxypteridine (No. 19) which has three additional nitrogen atoms. Because of their poor solubility, it was not possible to determine all the ionization and stability constants of the allyl and propyl derivatives of 8-hydroxyquinazoline, but they should be similar to those of 4-methyl-8-hydroxyquinazoline (No. 12).



Formation curves of metal complexes:
A, Copper complex of 8-hydroxy-1 : 7-naphthyridine.
B, Copper complex of 4-hydroxy-1 : 5-naphthyridine.
C, Ferrous complex of 8-hydroxy-1 : 6-naphthyridine.
[Sc] *and* $\bar{n}$ *are defined in Table 2.*

The order of magnitude of the stability constants is in most cases $Cu^{2+} > Ni^{2+} > Fe^{2+}$. This order has been shown to hold for a wide variety of complex-forming agents (Mellor and Maley, *Nature*, 1948, **161**, 436; Irving and Williams, *ibid.*, 1948, **162**, 764; Albert, *Biochem. J.*, 1950, **47**, 531; 1952, **50**, 690). However the naphthyridines chelate with ferrous ions and nickel ions with comparable avidity.

As Table 2 indicates, the difference between the logarithms of the partial stability constants K' and K'' ($\log K'' = \log K_s - \log K'$) is rarely larger than one unit for the analogues of 8-hydroxyquinoline, whereas it is never less than 1·7 units for 8-hydroxyquinoline. Thus, the introduction of additional nitrogen atoms into 8-hydroxyquinoline diminishes the tendency for complex formation to proceed by the successive addition of ligand molecules to the metallic ion and a certain amount of simultaneous addition takes place.

The formation curves (Figure) of the complexes of the hydroxynaphthyridines differ from the formation curves of the remaining analogues by exhibiting an anomalous increase in the value of $\bar{n}$ (shown in the Figure by a broken line) at low values of [Sc]. This effect, which occurs only when the pH is less than 1 unit above the basic pK_a of the chelating agent, must be ascribed to complex formation by the cationic species of the molecule.

These cations, because of the electron-attracting property of their positively charged nitrogen atoms, are stronger acids than the corresponding neutral molecules, and hence can provide a given concentration of the chelating species (in this case a zwitterion) at a lower pH (cf. 8-hydroxy-1 : 6-naphthyridine methiodide in Table 3 as an example of this effect). It follows from the Figure that the basic centres of the three hydroxynaphthyridines (Nos. 5, 6, and 7) are respectively $N_{(5)}$, $N_{(6)}$, and $N_{(7)}$, because if in any instance the basic centre were $N_{(1)}$, the cationic species would be incapable of chelation

TABLE 3. *Chelation of quaternary analogues of 8-hydroxyquinoline with* Ni^{2+}.

Compound	Acidic pK_a (0·01M; 20°)	log K_s (20°)
8-Hydroxyquinazoline 3-methiodide	7·26 (± 0·03)	8·4
5-Hydroxyquinoxaline 1-methiodide	5·74 (± 0·02)	9·5
8-Hydroxy-1 : 6-naphthyridine 6-methiodide	4·34 (± 0·03)	*ca.* 11

It has frequently been suggested that the stability of metal complexes should increase when the basic strength of the nitrogen atom is increased, or when the acidic strength of the hydroxyl group is decreased (Phillips and Merritt, *J. Amer. Chem. Soc.*, 1949, **71**, 3984; Bjerrum, *Chem. Reviews*, 1950, **46**, 381). An attempt was made, therefore, to interpret differences in complex-forming ability among the simpler analogues of 8-hydroxyquinoline in terms of the pK_a values of the hydroxyl groups and of the nitrogen atoms involved in chelation. Location of the basic centre in each analogue was thus required. Preparation of the methiodides of 8-hydroxyquinazoline, 5-hydroxyquinoxaline, and 8-hydroxy-1 : 6-naphthyridine revealed that all these quaternary salts were able to form strongly bound nickel complexes (Table 3).

The basic centres of the compounds from which they were derived must therefore be $N_{(3)}$, $N_{(1)}$, snd $N_{(6)}$ respectively. Hence, a comparison of basic and acidic strength with chelating ability among the present series of analogues of 8-hydroxyquinoline would involve measurement of the lower basic pK_a of each analogue, and this has not yet been attempted. However, Tables 2 and 3 show that conversion of 5-hydroxyquinoxaline and 8-hydroxyquinazoline into quaternary salts causes a large reduction in the stability of the nickel complexes. This is consistent with the above hypothesis since in each case quaternization not only increases the acid strength of the hydroxyl group, but also must weaken the basic strength of $N_{(1)}$ by a coulombic effect.

Oil–Water Partition of Complexes.—It is interesting to know what relation exists between the lipoid-solubility of the analogues and that of the corresponding 1 : 2 complexes. The direct determination of the partition coefficients of these complexes is beset with difficulties. However, an approach to the problem was made by examining the percentage of analogue extracted from 0·0002M-aqueous solution by oleyl alcohol in the absence and presence of nickel ions. The total amount of analogue (combined and free) was estimated in the aqueous layer (spectrophotometrically as free analogue after liberation by dilution in 0·1N-hydrochloric acid). These extractions were repeated with 0·001M-solutions to make sure that saturation of the oleyl alcohol was not occurring.

TABLE 4. *Effect of metallic ions on the extraction of analogues of 8-hydroxyquinoline from aqueous solutions* (25 *ml.*; 0·0002M) *by oleyl alcohol* (2 *ml.*) *at* 20° *and* pH 5·6—6·6.

No.	Substance (as sodium salt)	Extraction (%) Ni^{2+} present (0·0001M)	Extraction (%) Ni^{2+} absent	Oil–water partition coeff. (from Table 1)
11	8-Hydroxy-4-methylcinnoline ...	87	56	16·3
2	8-Hydroxycinnoline	57	31	5·6
3	8-Hydroxyquinazoline	33	29	5·2
5	4-Hydroxy-1 : 5-naphthyridine	15	0	<0·02
6	8-Hydroxy-1 : 6-naphthyridine	20	7	1·0
7	8-Hydroxy-1 : 7-naphthyridine	10	1	0·14

Table 4 shows that the amount of analogue extracted in the presence of nickel always exceeds that extracted in its absence. A valid comparison between two substances can be made only where they have comparable pK_a values and comparable K_s values. Such a pair are Nos. 2 and 11. Here the presence of a methyl group has enhanced both extractions by roughly the same factor. Unfortunately it was not possible to examine more analogues by this method: the complexes of Nos. 8—10 and 19 were not appreciably

lipoid-soluble, whereas those of Nos. 1, 13, and 14 were so highly lipoid-soluble that a measurable amount could not be retained in the aqueous phase. Nevertheless, these findings provide some measure of support for the concept that the partition coefficients of metal-binding agents provide a guide to the lipoid-solubility of the complexes.

Experimental

Microanalyses were by Mr. P. R. W. Baker, Beckenham.

The solubility data in Table 1 were obtained by dilution of saturated aqueous solutions in 0·1N-sodium hydroxide and spectrometric comparison with standard solutions of the substances in sodium hydroxide of the same concentration.

Ionization constants were determined potentiometrically as described by Albert, Brown, and Cheeseman (*J.*, 1951, 474).

Stability Constants.—Titrations were carried out by adding 0·1N-potassium hydroxide (carbonate-free; 2·5 ml.) in ten equal portions to 0·0025M-aqueous solutions (100 ml.) of the analogues containing 1 equiv. of the appropriate metallic ion. Prior addition of hydrochloric acid (as much as 4 equivs.) was sometimes necessary to reveal the lower values of $\bar{n}$. Titrations with ferrous ions were carried out in boiled-out water under nitrogen. Calculations of the stability constants were carried out as described by Albert (*Biochem. J.*, 1950, **47**, 531; 1952, **50**, 690).

All the analogues formed red complexes with ferrous ions, and greenish- or reddish-black complexes with ferric ions (as in the case of 8-hydroxyquinoline), except that Nos. 5, 7, and 9 gave orange ferric complexes. Copper complexes were pale green, except those of Nos. 2, 3, and 4 which were yellow. Nickel complexes of Nos. 5, 7, and 8 were pale green, of No. 2 red, and of the remainder yellow.

Partition Coefficients.—Pure oleyl alcohol (b. p. 132°/0·03 mm., n_D^{20} 1·4608) was obtained by fractionating commercial oleyl alcohol in a 100-cm. Vigreux column (heated jacket), the reflux ratio being kept at about 5. The copious initial fractions (b. p. 105—125°/0·03 mm.) consisted mainly of cetyl alcohol.

A solution of each compound (10^{-3}M or $0·2 \times 10^{-3}$M) in M/20-phosphate buffer (pH 7·3; 3—25 ml.) was gently shaken until equilibrated (3 hr.) with a volume (2—20 ml.; measured by weight) of oleyl alcohol sufficient to extract 10—90% of the compound from the aqueous phase. After centrifugation, the upper layer of oleyl alcohol was sucked off, and residual droplets of oil were removed by pouring the aqueous solution through a small pad of cotton wool. The concentration of the compound in the aqueous phase before and after extraction was found spectroscopically by making suitable dilutions in 0·1N-sodium hydroxide. Each extraction was repeated at a 2- or 5-fold dilution; in every instance the value of the partition coefficient was in good agreement with the value obtained from the more concentrated solution. Those partition coefficients having a value greater than 1 should not be in error by more than ±5%.

3-Methoxy-2-nitroacetophenone.—Condensation of 3-methoxy-2-nitrobenzoyl chloride (Curd, Landquist, and Rose, *J.*, 1948, 1764) with ethoxymagnesiomalonic ester in benzene solution, followed by hydrolysis and decarboxylation of the resulting acylmalonic ester in boiling propionic acid (cf. Bowman, *J.*, 1950, 322), gave this ketone, m. p. 128°, in 95% yield.

2-Formamido-3-methoxyacetophenone (I; R = Me).—2-Amino-3-methoxyacetophenone (2·24 g.; Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646) was added in portions, with shaking, during 15 min. to acetic formic anhydride (11 ml.; b. p. 29—32°/20 mm.; Béhal, *Compt. rend.*, 1889, **128**, 1460) at 0—5°. The solution was kept at 0—5° for a further 10 min., then poured on crushed ice. The pH was adjusted to 4 with 8N-ammonia, giving a white precipitate (1·31 g.) of *2-formamido-3-methoxyacetophenone*. An additional quantity (1·25 g.) was obtained by extracting the filtrate with chloroform (4 × 10 ml.), washing the extract with saturated aqueous sodium hydrogen carbonate (5 ml.), and evaporating the dried chloroform layer. The total yield was 97%. The compound formed colourless needles, m. p. 95°, from 600 parts of light petroleum (b. p. 60—80°) (Found: C, 62·2; H, 5·7; N, 7·3. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%).

8-Methoxy-4-methylquinazoline (II; R = Me).—A stream of dry ammonia was passed for 3 hr. into a solution at 155—160° (bath-temp.) of the above formyl derivative (2 g.) in molten ammonium acetate (20 g.). Water (100 ml.) was added to the cooled mixture and the product (1·5 g., 83%; m. p. 129—130°) collected. Crystallization from water (50 parts) gave *8-methoxy-4-methylquinazoline* as colourless needles, m. p. 131° (Found, for material dried at 80°: C, 68·7; H, 5·5; N, 16·1. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

8-*Hydroxy*-4-*methylquinazoline*.—An intimate mixture of 8-methoxy-4-methylquinazoline (0·5 g.) and anhydrous aluminium chloride (1·5 g.) was heated at 100° (vigorous reaction !). The orange product was heated for 4 hr. at 130—135°, cooled, and dissolved in water (15 ml.). The solution was brought to pH 3—4 and extracted continuously with ether for 6 hr. The dried ethereal layer was evaporated and the gummy residue triturated with water (3 ml.), at pH 5, giving a yellow powder (0·30 g., 65%; m. p. 158—159°). Sublimation at 140—150°/25 mm., followed by crystallization from light petroleum (b. p. 60—80°; 65 ml.), gave cream-coloured needles (0·23 g.), m. p. 162°, of 8-*hydroxy*-4-*methylquinazoline* (Found: C, 67·4; H, 5·0; N, 17·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

3-*Methoxy*-2-*nitrophenyl Propyl Ketone*.—A solution of 3-methoxy-2-nitrobenzoyl chloride (10·8 g., 0·05 mole) in benzene was slowly added, with shaking, to a benzene solution (20°) of dibenzyl sodioethylmalonate (0·05 mole; prepared from diethyl ethylmalonate by Bowman's method, *J.*, 1950, 325). The mixture was refluxed for 30 min., cooled, and poured into water containing a trace of sulphuric acid. The aqueous layer was separated and extracted with benzene (2 × 20 ml.). The benzene was washed with water (2 × 30 ml.), dried (Na_2SO_4), and evaporated under reduced pressure (finally at 100°/0·05 mm.), giving crude dibenzyl ethyl-(3-methoxy-2-nitrobenzoyl)malonate (24·1 g.) as a thick red gum. This was hydrogenated in ethyl acetate (100 ml.) over 10% palladium–strontium carbonate (2 g.; prepared according to Bowman, *loc. cit.*). The catalyst was filtered off, and the solution refluxed for 3 hr., cooled to 20°, and filtered from 3-methoxy-2-nitrobenzoic acid (0·7 g.). Removal of the ethyl acetate under reduced pressure and trituration of the residual gum with N-sodium hydroxide (100 ml.) gave a fawn-coloured solid, m. p. 73—78°. Crystallization of this from light petroleum (b. p. 60—80°; 200 ml.), then from methanol (4 ml.), yielded colourless prisms (2·8 g.), m. p. 82°, of 3-*methoxy*-2-*nitrophenyl propyl ketone* (Found: C, 59·2; H, 5·7; N, 6·4. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%).

2-*Formamido*-3-*methoxyphenyl Propyl Ketone* (I; R = Pr^n).—Iron filings (3·25 g.) were added during 1 hr. to a stirred solution of the above ketone (2·6 g.) in acetic acid (12·5 ml.) on the steam-bath. Water (12·5 ml.) was added in 2·5-ml. portions at 15 min. intervals. The mixture was heated for 1 hr. more, then diluted with water (50 ml.) and extracted with ether (4 × 25 ml.). The ethereal layer was washed with 2N-sodium carbonate (20 ml.). Removal of the ether from the dried (Na_2SO_4) solution and distillation of the residue gave 2-amino-3-methoxyphenyl propyl ketone (2·15 g., 95%) as a yellow oil, b. p. 82—84°/0·02 mm. Reaction of this amine with acetic formic anhydride as described above gave 99% (m. p. 36°) of 2-*formamido*-3-*methoxyphenyl propyl ketone* which formed colourless prisms, m. p. 37—37·5°, from 250 parts of light petroleum (b. p. 40—50°) (Found: C, 65·3; H, 6·6; N, 6·3. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

8-*Methoxy*-4-*propylquinazoline* (II; R = Pr^n).—This formyl derivative (0·2 g.) was heated for 8 hr. at 150—160° in a sealed tube with ethanolic ammonia (2 ml.; saturated at 0°). The alcohol was distilled off and 2N-sodium hydroxide (10 ml.) added to the residue. The mixture was extracted with light petroleum (b. p. 60—80°; 5 × 10 ml.), and the extract was washed with N-sodium hydroxide (10 ml.) and then evaporated, giving 8-*methoxy*-4-*propylquinazoline* (0·17 g., 93%), m. p. 35—36°. The compound formed yellow needles, m. p. 38—39°, from light petroleum (b. p. 40—60°; 10 ml., concentrated to 2 ml.) (Found: C, 71·4; H, 6·9; N, 13·9. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 7·0; N, 13·9%).

8-*Hydroxy*-4-*propylquinazoline*.—8-Methoxy-4-propylquinazoline (0·45 g.) and anhydrous aluminium chloride (1·5 g.) were heated for 4 hr. at 130—135°. The cooled mixture was decomposed by the addition of water (15 ml.). An excess of 40% aqueous sodium hydroxide was added, and the yellow precipitate collected at 0°, washed with 2N-sodium hydroxide, and dissolved in water (30 ml.). The solution was adjusted to pH 7, giving a precipitate of 8-*hydroxy*-4-*propylquinazoline* (0·27 g., 64%), m. p. 99—100°. Crystallization from light petroleum (b. p. 40—60°; 25 ml., concentrated to 3 ml.) gave pale yellow needles (0·25 g.), m. p. 100° (Found: C, 70·2; H, 6·5; N, 14·9. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

8-*Allyloxyquinazoline*.—Allyl bromide (1·7 g.) was added to a solution prepared from 8-hydroxyquinazoline (2 g.) and potassium (0·54 g.) in absolute methanol (10 ml.), and the mixture refluxed for 6 hr. After removal of the methanol, 2N-sodium hydroxide (10 ml.) was added and the mixture extracted with chloroform. The chloroform layer was dried (K_2CO_3) and evaporated under reduced pressure. Distillation of the residue gave an oil, b. p. 98—100°/0·04 mm., which on cooling formed colourless needles (1·67 g., 65%), m. p. 53—54°, of 8-*allyloxyquinazoline*. When crystallized from 80 parts of light petroleum (b. p. 40—60°) the product melted at 55° (Found: C, 71·0; H, 5·4; N, 15·4. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

7-Allyl-8-hydroxyquinazoline.—8-Allyloxyquinazoline (0·6 g.) was heated for 10 min. at 195—200°. A solution of the product in N-sodium hydroxide (25 ml.) was extracted with benzene (2 × 10 ml.) (upper layer rejected), and adjusted to pH 6. The precipitate of fawn-coloured crystals (0·5 g., 83%), m. p. 108—109°, when crystallized from light petroleum (b. p. 60—80°; 20 parts) gave colourless plates (0·44 g.) of *7-allyl-8-hydroxyquinazoline*, m. p. 109·5° (Found: C, 71·3; H, 5·5; N, 15·1. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

Methiodides.—8-Hydroxyquinazoline (0·5 g.) and methyl iodide (3 ml.) were heated at 100° for 3 hr. in a sealed tube. The product was washed with chloroform and crystallized from ethanol (25 ml.; concentrated to 10 ml.), giving colourless needles (0·51 g.), m. p. 192° (decomp.), of the *monoalcoholate* of *8-hydroxyquinazoline 3-methiodide* (Found: C, 40·1; H, 4·5; N, 8·3; I, 37·3. $C_9H_9ON_2I,C_2H_6O$ requires C, 39·6; H, 4·5; N, 8·4; I, 38·0%). When heated at 100°, the product lost the alcohol.

Treatment of 5-hydroxyquinoxaline (0·25 g.) with methyl iodide as described above gave *5-hydroxyquinoxaline 1-methiodide*, orange plates (0·40 g.), m. p. 177° (decomp.) [from *n*-propanol (22 ml.)] (Found, for material dried at 110°: C, 38·2; H, 3·2; N, 9·6. $C_9H_9ON_2I$ requires C, 37·5; H, 3·2; N, 9·7%).

A suspension of finely ground 8-hydroxy-1 : 6-naphthyridine (0·4 g.) in methyl iodide (8 ml.) was heated at 85° for 1 hr. The orange solid was washed with chloroform, crystallized from water (5 ml.) (charcoal), and dried in a vacuum over potassium hydroxide, giving the orange *monohydrate* (0·6 g.), m. p. 165—167° (decomp.), of *8-hydroxy-1 : 6-naphthyridine 6-methiodide* (Found: C, 35·3; H, 3·7; N, 9·1. $C_9H_9ON_2I,H_2O$ requires C, 35·3; H, 3·6; N, 9·2%).

Other Materials.—4-Hydroxy-1 : 5-naphthyridine was prepared according to Klisiecki and Sucharda (*Roczn. Chem.*, 1927, **7**, 204; *Chem. Zentr.*, 1928, I, 2092). 4-Hydroxypyridino-(2′ : 3′ : 5 : 6)pyrimidine was prepared by Price and Curtin's method (*J. Amer. Chem. Soc.*, 1946, **68**, 914) in 70% yield.

THE DEPARTMENT OF MEDICAL CHEMISTRY, THE AUSTRALIAN NATIONAL UNIVERSITY,
183 EUSTON ROAD, LONDON, N.W.1. [*Received, September 19th*, 1953.]

Carcinogenic Nitrogen Compounds. Part XVI. Some Condensed Carbazoles and their Thiophen Analogues.*

By NG. PH. BUU-HOÏ and P. JACQUIGNON.

[Reprint Order No. 4760.]

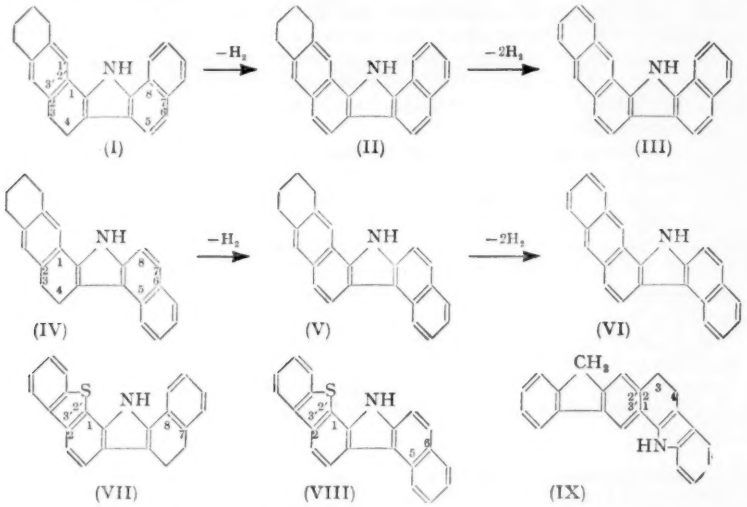
Some condensed derivatives of carbazole, their analogues in the thiophen series, and polycyclic indoles have been synthesised for testing as potential carcinogens and as tumour-growth inhibitors.

SEVERAL condensed carbazoles, especially 1 : 2-benzocarbazoles (Lacassagne, Buu-Hoï Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635) and bis-angular dibenzocarbazoles (Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Badger, Cook, Hewett, Kennaway, Kennaway, Martin, and Robinson, *ibid.*, 1942, **131**, 170; Kirby and Peacock, *Brit. J. Exp. Path.*, 1946, **27**, 179), have shown significant carcinogenic properties and inhibitory effects on the growth of grafted tumours (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255), and it was therefore considered of interest to synthesise some even more condensed carbazole derivatives for biological testing. The present paper reports the preparation of hexacyclic compounds.

The α-naphthylhydrazone of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-1-oxoanthracene was converted by hydrogen chloride in acetic acid (cf. Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, 1951, **16**, 315) into 3 : 4 : 5′ : 6′ : 7′ : 8′-hexahydro-7 : 8-benzonaphtho(2′ : 3′-1 : 2)-carbazole (I), which was partially dehydrogenated by use of 1·3 mols. of chloranil (cf. Barclay and Campbell, *J.*, 1945, 530; Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1949, **14**, 492) to the tetrahydro-compound (II); dehydrogenation by 5·5 mols. of chloranil afforded the fully aromatic (III). The same sequence of reactions was followed for the

* Part XV, *J.*, 1953, 3584.

preparation of 5 : 6-benzonaphtho(2′ : 3′-1 : 2)carbazole (VI). Indole formation from the α- and the β-naphthylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen (Buu-Hoï, and Cagniant, *Ber.*, **1943**, **76**, 1269) gave directly 7 : 8-benzo- (VII) and 5 : 6-benzothionaphtheno(2′ : 3′-1 : 2)carbazole (VIII), the intermediary dihydro-compounds being oxidised during the process.



Fischer cyclisation of 2- and 3-acetylphenanthrene phenylhydrazone readily gave 2-2′- and 2-3′-phenanthrylindole respectively; from 3-*n*-butyrylpyrene phenylhydrazone, 3-ethyl-2-3′-pyrenylindole was similarly prepared. The phenylhydrazone of 1′ : 2′ : 3′ : 4′-tetrahydro-4′-oxo-2 : 3-benzofluorene readily afforded 3 : 4-dihydro-compound (IX), but dehydrogenation of this compound in the usual way failed to give a pure product.

None of the substances described here showed carcinogenic activity in mice with the skin-painting technique.

Experimental

3 : 4 : 5′ : 6′ : 7′ : 8′-*Hexahydro*-7 : 8-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (I).—1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-Octahydro-1-oxoanthracene, b. p. 206—207°/18 mm., m. p. 48°, was prepared from tetralin and succinic anhydride according to Krollpfeiffer and Schäfer (*Ber.*, 1923, **56**, 620), except that the β-(1 : 2 : 3 : 4-tetrahydro-1-naphthoyl)propionic acid was reduced with hydrazine hydrate and potassium hydroxide in diethylene glycol (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2478). A solution of this ketone (2 g.), α-naphthylhydrazine hydrochloride (2·6 g.), and sodium acetate (1·5 g.) in ethanol was refluxed for 1 hr., and the crude hydrazone obtained on dilution with water was treated with a boiling acetic acid solution of hydrogen chloride (20 c.c.). The precipitated *carbazole* derivative obtained on dilution with water gave on recrystallisation yellowish needles (2 g.), m. p. 187°, from benzene (Found : C, 88·8; H, 6·5. $C_{24}H_{21}N$ requires C, 89·2; H, 6·5%), giving yellow sulphuric acid solutions and a violet picrate.

5′ : 6′ : 7′ : 8′-*Tetrahydro*-7 : 8-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (II).—A solution of the foregoing substance (1 g.) and chloranil (1 g.) in dry xylene (30 c.c.) was refluxed for 2 hr.; the tetrachloroquinol was filtered off after cooling, and the filtrate washed with dilute aqueous sodium hydroxide and with water. The solid *tetrahydro*-compound obtained after removal of solvent formed pale yellow needles (0·7 g.), m. p. 217°, from benzene (Found : C, 89·4; H, 5·8. $C_{24}H_{19}N$ requires C, 89·7; H, 5·9%), giving a cherry-red sulphuric acid solution and a brown-violet picrate.

7 : 8-*Benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (III).—A solution of compound (I) (0·8 g.) and chloranil (3 g.) in dry xylene (50 c.c.) was treated as above; the dehydrogenation *product* (0·5 g.)

formed shiny greenish-yellow leaflets, m. p. 282°, from benzene, giving a violet colour with sulphuric acid (Found: C, 90·4; H, 4·8; N, 4·3. $C_{24}H_{15}N$ requires C, 90·8; H, 4·7; N, 4·4%).

3 : 4 : 5′ : 6′ : 7′ : 8-*Hexahydro*-5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (IV).—Prepared as for the isomer (I), this *compound* formed from benzene yellowish prisms, m. p. 211° (Found: C, 88·9; H, 6·5%), giving orange sulphuric acid solutions and a violet picrate.

It gave **5′ : 6′ : 7′ : 8′-*tetrahydro*-5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole*** (V), pale yellow needles (from benzene), m. p. 260°, giving brown-red sulphuric acid solutions (Found: C, 89·5; H, 5·7%), and thence **5 : 6-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole*** (VI), greenish-yellow leaflets (from xylene), m. p. 311°, giving a brown-violet colour with sulphuric acid (Found: C, 90·5; H, 4·5%).

7 : 8-*Benzothionaphtheno*(2′ : 3′-1 : 2)*carbazole* (VII).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxodibenzothiophen (1·5 g.), α-naphthylhydrazine hydrochloride (3 g.), and sodium acetate (3 g.) was refluxed for 1 hr. in ethanol, and the crude hydrazone obtained was cyclised in the usual way (slight decomposition with evolution of hydrogen sulphide occurred during this process). The *carbazole* (1·3 g.) crystallised as shiny, grey-tinged leaflets, m. p. 266°, from benzene, giving brown-red sulphuric acid solutions (Found: C, 80·8; H, 4·6. $C_{22}H_{15}NS$ requires C, 81·2; H, 4·6%). This substance was recovered unchanged after treatment with chloranil.

5 : 6-*Benzothionaphtheno*(2′ : 3′-1 : 2)*carbazole* (VIII), prepared therefrom, crystallised as grey-tinged prisms (1·5 g.), m. p. 306°, from benzene (Found: C, 81·9; H, 4·5%), giving brown-red sulphuric acid solutions, and a red picrate.

3 : 4-*Dihydrofluoreno*(3′ : 2′-1 : 2)*carbazole* (IX).—1′ : 2′ : 3′ : 4′-Tetrahydro-4′-oxo-2 : 3-benzofluorene, m. p. 148—149°, b. p. 279—280°/21 mm., was prepared from fluorene and succinic anhydride according to Koelsch (*J. Amer. Chem. Soc.*, 1933, **55**, 3885), except that the intermediary keto-acid was reduced by the Huang-Minlon technique. A mixture of the ketone (4 g.) and phenylhydrazine was heated at 120° with removal of water, and the crude hydrazone cyclised in the usual way; the *carbazole* formed colourless prisms (4 g.), m. p. 140°, from ethanol (Found: C, 89·7; H, 5·6. $C_{23}H_{17}N$ requires C, 89·9; H, 5·5%), giving a yellow colour with sulphuric acid, and a deep violet picrate.

2-2′-*Phenanthrylindole*.—A mixture of 2-acetylphenanthrene phenylhydrazone (6 g.; yellowish needles, m. p. 190—191°, from ethanol) and freshly fused zinc chloride was heated at 200° until the reaction had subsided; aqueous acetic acid was added, and the *indole* taken up in benzene. It crystallised as grey-tinged prisms (4 g.), m. p. 237°, from ethanol (Found: C, 90·0; H, 5·3. $C_{22}H_{15}N$ requires C, 90·1; H, 5·1%). The corresponding picrate formed brown-violet needles, m. p. 205—206°, from ethanol.

2-3′-*Phenanthrylindole*.—Similar cyclisation of 3-acetylphenanthrene phenylhydrazone (6·5 g.; yellowish needles, m. p. 188—189°, from ethanol) yielded an *indole*, crystallising as grey-tinged prisms (5 g.), m. p. 160°, from ethanol (Found: C, 89·8; H, 5·1%), giving a brown-violet picrate.

3-*Ethyl*-2-3′-*pyrenylindole*.—Cyclisation of 3-*n*-butyrylpyrene phenylhydrazone (3 g.), effected with acetic acid and hydrogen chloride, afforded an *indole*, crystallising from ethanol as yellowish needles, m. p. 147° (Found: C, 90·1; H, 5·4. $C_{26}H_{19}N$ requires C, 90·4; H, 5·5%), giving a red picrate.

This work forms part of a cancer research scheme (Professor A. Lacassagne) financially supported by the United States Public Health Service (Federal Security Agency); the authors thank the authorities concerned, also Mr. D. H. Chuong for assistance.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, October* 31*st*, 1953.]

Michael Condensations with Substituted Sorbic Esters. Part I. Methyl β-iso*Butenyl-*αα′*-dimethoxycarbonylglutarate.*

By Evans B. Reid and H. William Sause.

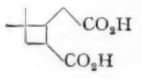
[Reprint Order No. 4682.]

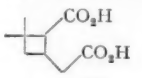
Dehydrobromination of 4-bromo-5-methylhex-2-enoic acid * and its methyl ester gave only low yields of the stereoisomeric δ-methylsorbic acids. Methyl δ-methylsorbate and methyl 5-methylhex-2-enoate failed to undergo Michael condensation with methyl malonate or methyl cyanoacetate. New syntheses of methyl α-cyano- and α-methoxycarbonyl-δ-methylsorbate are described. Michael condensation of the latter with malonic ester occurs by αβ-addition to at least 83% extent, giving methyl β-*iso*butenyl-αα′-dimethoxycarbonylglutarate. The glutaric ester adds hydrogen chloride to form a new chloro-ester, and with hydrogen bromide gives a bromo-ester that decomposes spontaneously by loss of methyl bromide to form a lactonic triester. Attempts to cyclise the chloro-ester with methyl sodio-*n*-propylmalonate yielded only products of dehydrochlorination and retro-Michael reactions. Acid hydrolysis of the Michael condensation product formed a new lactonic acid, and the latter with methanol formed the lactonic monoester and the corresponding unsaturated diester.

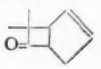
The experiments described in this paper were initiated several years ago with a view to develop an unambiguous synthesis of the second of the two isomeric formulations (I and II), and thus to reach a decision regarding the structure of caryophyllenic acid (Ruzicka and Zimmerman, *Helv. Chim. Acta*, 1935, **18**, 219; Ramage and Simonsen, *J.*, 1935, 532).

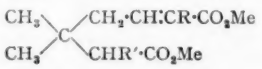
In an attempted synthesis of (II) from the dimethyl*bicyclo*heptenone (III) (Ramage and Simonsen, *Chem. and Ind.*, 1939, **58**, 447) difficulty was encountered in effecting complete reduction of the carbonyl group. However the later successful completion of this reduction by Dawson and Ramage (*J.*, 1950, 3523) indicated that caryophyllenic acid was (I), and this was confirmed by its direct synthesis by Campbell and Rydon (*Chem. and Ind.*, 1951, 312).

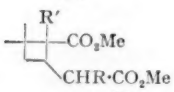
The present investigation sought an approach to structure (IV; R = H, CN, or CO_2Me; R′ = CN or CO_2Me), since internal Michael condensation should lead to the *cyclo*butane derivative (V) (cf. Ingold, Perren, and Thorpe, *J.*, 1922, **121**, 1765), and the latter on hydrolysis and decarboxylation would furnish the acid (II).


(I)


(II)


(III)


(IV)


(V)

$CHMe_2{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2R$
(VI)

$CMe_2{:}CH{\cdot}CH{:}CH{\cdot}CO_2R$
(VII)

5-Methylhex-2-enoic acid * (VI; R = H), best prepared by the Knoevenagel reaction of *iso*valeraldehyde with malonic acid in pyridine (von Auwers, *Annalen*, 1923, **432**, 50, 79), reacted readily with *N*-bromosuccinimide to give a bromo-acid that was dehydrobrominated only poorly by pyridine, and other bases, to furnish the stereoisomeric δ-methylsorbic acids (VII; R = H). Attempted Michael condensation of methyl malonate or cyanoacetate with methyl 5-methylhex-2-enoate (VI; R = Me) or δ-methylsorbate (VII; R = Me) failed. The sorbate was of special interest in view of Bloom and Ingold's speculation (*J.*, 1931, 2765) that δδ-dialkyl substitution in the diene system should favour formation of αβ-addition products at the expense of αδ-addition. It appeared entirely likely, however, that the inertia of the diene system in methyl δ-methylsorbate

* Geneva nomenclature, CO_2H = 1.

could be overcome by the suitable incorporation of additional electrophilic groups. Bloom and Ingold (*loc. cit.*) had indeed found that in the Michael condensation of cyanoacetic ester with sorbic ester and with crotonylidenemalonic ester, 10% of the total reaction occurred αβ-positions in the first case, and 16% in the second. Thus it seemed that methyl α-cyano- (VIII) or α-methoxycarbonyl-δ-methylsorbate (IX) might be suitable progenitors for the ultimate preparation of (IV), although it was realised that both δδ-dialkyl substitution and the αβ-situated electron sink should undoubtedly induce some αβ-addition and thus lessen the yield of the desired αδ-product.

The starting material for the synthesis of (VIII) and (IX) was β-methylcrotonaldehyde, best prepared by bromination of *iso*valeraldehyde and dehydrobromination (Fischer, Ertel, and Löwenberg, *Ber.*, 1931, **64**, 30; Fischer and Löwenberg, *Annalen*, 1932, **494**, 280). For the preparation of the sorbic esters, the acetal of β-methylcrotonaldehyde was hydrolysed with the theoretical quantity of water, acetic acid being used as catalyst as in the procedure of Cope *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 3452) for the preparation of alkylidenemalonic esters. Direct addition of piperidine and malonic or cyanoacetic ester to the hydrolysis mixture allowed the synthesis to be carried out without the usual loss occasioned by the isolation of the intermediate aldehyde.

Methyl α-cyano-β-methylsorbate (VIII) was isolated as a colourless crystalline substance, m. p. 74·5—75°. Andrews *et al.* (*ibid.*, 1945, **67**, 715) describe it as a yellow compound, m. p. 70·5—75°. The product, however, in typical Michael condensations gave inconclusive results in that only red acidic gums could be isolated from hydrolysis of the crude Michael products.

Methyl α-methoxycarbonyl-δ-methylsorbate (IX) was obtained as a colourless oil possessing a relatively high refractive index. The structure of this diene was clearly established by catalytic hydrogenation followed by hydrolysis and decarboxylation to 5-methylhexanoic acid, identical with that obtained by reduction and hydrolysis of methyl 5-methylhex-2-enoate (VI; R = Me).

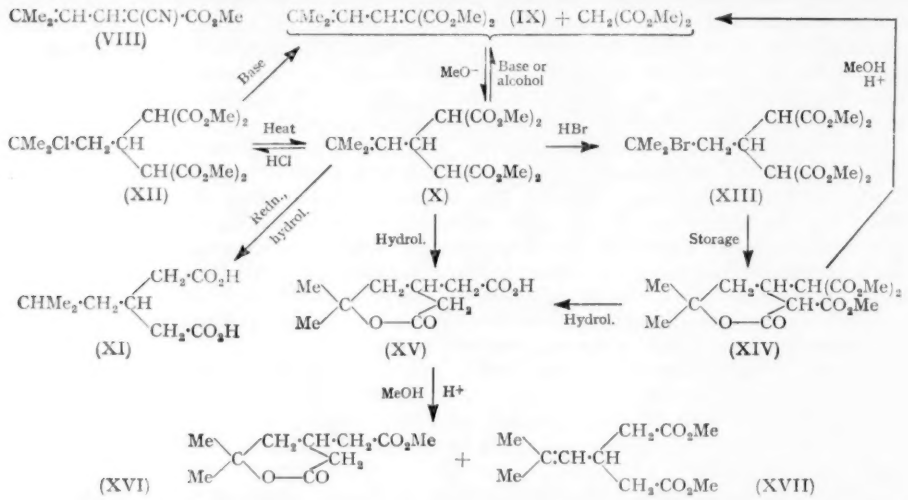
Under the conditions prescribed by Koelsch (*ibid.*, 1943, **65**, 437) the dicarboxy-ester (IX) reacted readily with methyl malonate and sodium methoxide to yield methyl β-*iso*but-2-enyl-αα′-dimethoxycarbonylglutarate (X) as a viscous almost colourless oil. The *exclusive* formation of this αβ-addition product (at least 83% yield) was surprising, and critically hindered our approach to the acid (II) although several attempts were made to transform this substance into the *cyclo*butane derivative (V). The reactions used to substantiate the structure of this Michael adduct, and the various transformations encountered in this work are set forth in the reaction scheme annexed.

The Michael product (X) proved to be exceedingly sensitive. It undergoes a complete retro-Michael reaction not only on contact with base, but also in the presence of alcohol. The latter reaction occurred during an unsuccessful attempt to reduce the compound in presence of Adams's catalyst and methanol. The products recovered were the sorbic ester (IX) and methyl malonate. For the successful reduction of the compound it was necessary to use massive amounts of Adams's catalyst in glacial acetic acid. Acid hydrolysis of the resulting dihydro-ester gave β-*iso*butylglutaric acid (XI), isolated as the anhydride in 87% overall yield from the glutaric ester (X). For comparison authentic anhydride was prepared (Curtis *et al.*, *J.*, 1923, **123**, 3131). Substantiation of αβ-addition was also secured by ozonolysis of (X), giving small yields of tricarballylic acid.

Acid hydrolysis of the Michael addition product furnished the crystalline lactonic acid (XV), whose structure is based upon analysis, titration, and the assumption of a normal Markovnikov addition of water to the ethylenic bond of the glutaric ester (X). Esterification of the lactonic acid with methanol–acid gave a 51% yield of the lactonic ester (XVI), together with a 28% yield of methyl β-*iso*butenylglutarate (XVII). It may be noted that the lower yield of the diester (XVII) implies formation of this compound from the lactonic ester by acid-catalysed dehydration of the intermediate tertiary alcohol.

With the structure of the Michael adduct established it seemed desirable to ascertain whether the Thorpe–Ingold effect (Ingold, *J.*, 1925, **127**, 387), so prominent in the α-halogeno-glutaric acid series, would be operative in promoting cyclisations involving internal alkylation of the malonic ester group in the glutarate (X). Boron trifluoride

was without effect on (X), and our attention then turned to attempted cyclisations of the hydrogen halide derivatives.



In carbon tetrachloride, (X) readily absorbed 1 mol. of hydrogen chloride to form the crystalline chloro-derivative (XII), which, in contradistinction to the ester of β-chloro-γ-methylvaleric acid (Bredt, *Ber.*, **1886**, **19**, **513**), was unstable to heat and could not be distilled *in vacuo* without quantitative loss of hydrogen chloride to regenerate the glutaric ester (X). Ring closure of the chloro-ester (XII) by internal alkylation was attempted by equilibrating the chloro-ester in xylene with ethyl sodio-*n*-propylmalonate. The choice of this reagent was based upon the facts that it was soluble in xylene, that it would be sterically unsuitable for intermolecular alkylation with the chloro-ester, and that it should form an anion of approximately the same basic strength as the anion derived from a malonic group within the chloro-ester itself. The latter, on displacement of the chloride ion might then be expected to undergo cyclisation. Actually the products of this reaction resulted from dehydrochlorination followed by a retro-Michael reaction, giving the sorbic ester (IX) together with methyl malonate and ethyl *n*-propylmalonate.

In view of the lower electrophilic nature of bromine, it appeared that use of the corresponding bromo-ester might be more profitable. However, although the Michael adduct readily reacted with hydrogen bromide in carbon tetrachloride, the bromo-ester (XIII) spontaneously lost methyl bromide on concentration of the solution, yielding the crystalline lactone (XIV), whose structure was readily proved by acid hydrolysis to the lactonic acid (XV). Attempts to regenerate the bromo-ester (XIII) by the action of methanolic hydrogen bromide gave only methyl malonate and methyl α-methoxycarbonyl-δ-methylsorbate (IX), resulting from a retro-Michael reaction of the glutarate (X), which must be assumed to be an intermediate in the last reaction. It may be noted that this behaviour of the lactonic ester (XIV) is different from that of the simple γ-methyl-γ-valerolactone (Bredt, *loc. cit.*) which on treatment with alcoholic hydrogen bromide readily yields its γ-bromo-ester, the latter regenerating the lactone only on distillation. The differences between the behaviour of the simple γ-methylvaleric models and our more involved *iso*-butenylglutaric esters are obviously due to the intense driving force of the retro-Michael reaction which furnishes the conjugated methyl α-methoxycarbonyl-δ-methylsorbate as the end-product.

Experimental

δ-Methylsorbic Acid (VII; R = H).—**5-Methylhex-2-enoic** acid (VI; R = H) (**11·3 g.**, 0·0885 mole), prepared according to von Auwers (*loc. cit.*), in carbon tetrachloride (**35 ml.**) was

treated with *N*-bromosuccinimide (15·75 g., 0·0885 mole), reaction being started by warming (infra-red lamp). Succinimide was separated by filtration, and the filtrate was washed with water, dried, and distilled. The bromo-acid (14·2 g.) boiled at 115—124°/3 mm. It was dissolved in 18·5 ml. of pyridine and, after being kept overnight, refluxed for 15 min. The resultant crystalline mass was dissolved in ether and dilute sulphuric acid. The ethereal solution was freed from pyridine by washing it with dilute acid and was then extracted with sodium hydroxide solution. A chloroform extract of the acidified aqueous solution furnished a mixture of oil and solid on evaporation. Recrystallisation of the solid from hexane yielded *trans*-δ-methylsorbic acid (3·8 g.), m. p. 104·5—105° (Found: C, 66·5, 66·5; H, 8·0, 8·0. Calc. for $C_7H_{10}O_2$: C, 66·6; H, 8·0%).

Esterification of the acid in methanol and ethylene dichloride with sulphuric acid (Clinton and Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135) gave *methyl δ-methylsorbate* (VII; R = Me), b. p. 79—79·5°/9·5 mm., $n_D^{21\cdot4}$ 1·5141 (Found: OMe, 22·3. $C_7H_9O{\cdot}OMe$ requires OMe, 22·1%).

Attempted Michael Reaction with Methyl δ-Methylsorbate.—A mixture of methyl δ-methylsorbate (3·94 g., 0·0281 mole) and methyl cyanoacetate (2·80 g., 0·0281 mole) in absolute methanol (10 ml.) containing 10 drops of piperidine became deep violet-red in 16 days. Only the starting materials and 0·5 g. of viscous, dark red oil were isolated on working up. Hydrolysis of the oil with 6N-hydrochloric acid gave a small amount of oil, not acidic to bicarbonate. Likewise, no evidence could be found of Michael reaction with methyl malonate. Methyl 5-methylhex-2-enoate (VI; R = Me) was also inert.

Methyl α-Cyano-δ-methylsorbate (VIII).—β-Methylcrotonaldehyde diethyl acetal (15·8 g., 0·1 mole) (Fischer, Ertel, and Löwenberg, *loc. cit.*) was hydrolysed with acetic acid (1·2 g., 0·02 mole) in water (1·8 g., 0·1 mole). After the addition of methyl cyanoacetate (9·9 g., 0·1 mole) and piperidine (0·17 g., 0·002 mole) the solution was set aside for 3 hr.; crystallisation was then induced by scratching. Methyl α-cyano-δ-methylsorbate was obtained as a colourless solid, m. p. 74·5—75° (Found: C, 65·2; H, 6·7; OMe, 18·7. Calc. for $C_8H_8ON{\cdot}OMe$: C, 65·4; H, 6·7; OMe, 18·8%).

To a solution of (VIII) (4 g., 0·024 mole) in methyl cyanoacetate (2·4 g., 0·024 mole) and a few ml. of methanol were added 4 drops of 2·17M-sodium methoxide. The solution became orange-red in 5 days. No evidence of a Michael addition product was obtained.

Methyl α-Methoxycarbonyl-δ-methylsorbate (IX).—β-Methylcrotonaldehyde diethyl acetal (15·8 g., 0·1 mole) was hydrolysed with glacial acetic acid (1·2 g., 0·02 mole) and water (1·8 g., 0·1 mole). After the addition of methyl malonate (13·2 g., 0·1 mole) the mixture was cooled in ice, and piperidine (0·34 g., 0·004 mole) was added. The solution was allowed to warm to room temperature and, after 36 hr., was diluted with ether and washed free from piperidine. The yield of *methyl α-methoxycarbonyl-δ-methylsorbate*, b. p. 107—110·5°/1·5 mm., n_D^{25} 1·5165, varied from 24 to 39% [Found: C, 58·8, 58·6; H, 7·2, 6·95; OMe, 31·1, 31·5. $C_8H_8O_2(OCH_3)_2$ requires C, 60·6; H, 7·1; OMe, 31·3%. 0·1825 G. of ester absorbed 0·00187 mole of hydrogen (Calc.: 0·00184 mole)].

Methyl β-iso*But*-1-*enyl*-αα′-*dimethoxycarbonylglutarate* (X).—Methyl malonate (13·6 g., 0·103 mole) was mixed with (IX) (20·37 g., 0·103 mole). After the addition of 9 drops of 3·26M-sodium methoxide, the mixture was set aside at room temperature for a few hours and then overnight at 5°. Ten drops of glacial acetic acid were added to the cold mixture, which was then taken up in ether, washed with dilute acid and water, dried, and evaporated. Fractionation of the residue yielded 25·94 g. (83%) of *methyl* β-iso*but*-1-*enyl*-αα′-*dimethoxycarbonylglutarate*, a pale yellow, viscous liquid, b. p. 122—132°/0·1 mm., $n_D^{25\cdot3}$ 1·4593 [Found: C, 54·6; H, 6·95; OMe, 37·2. $C_{11}H_{10}O_4(OCH_3)_4$ requires C, 54·5; H, 6·7; OMe, 37·6%].

Ozonolysis of (X) gave only a small yield of tricarballylic acid.

Hydrogenation of (X) could be achieved only by the use of Adams's catalyst in the proportion of 1·5 g. of catalyst to 4 g. of compound in 20 ml. of glacial acetic acid. Hydrolysis of the reduced ester and distillation of the product gave β-*iso*butylglutaric anhydride (87·4%), b. p. 150—156°/0·8 mm., n_D^{25} 1·4555 (Found: C, 63·3; H, 8·5. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%); the residue was a few drops of red oil.

The anilic acid prepared from the anhydride melted at 140—140·5°, undepressed on mixture with the anilic acid prepared from authentic β-*iso*butylglutaric anhydride.

β-(2-*Hydroxy*-2-*methylpropyl*)*glutaric Acid δ-Lactone* (XV).—The Michael product (X) (10·52 g., 0·032 mole) was refluxed overnight with 7N-hydrochloric acid (50 ml.) under nitrogen. Isolation of the acidic product yielded the *lactone*, m. p. 98·5—100° (corr.) (2·95 g.) (Found: C, 58·2; H, 7·4%; equiv., 93·6. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%; equiv., 93·1).

The lactonic acid (2·25 g., 0·01209 mole) was refluxed with methanol (2·94 ml., 0·0725 mole),

ethylene dichloride (7·26 ml.), and 2 drops of sulphuric acid, and the two esterification products were isolated in the usual manner, *viz.*: *methyl* β-*but*-1′-*enylglutarate* (XVII) (0·725 g., 28%), b. p. 101—113°/0·76 mm., n_D^{21} 1·4467 [Found: C, 61·2; H, 8·8; OMe, 29·1. $C_8H_{12}O_2(OMe)_2$ requires C, 61·7; H, 8·5; OMe, 29·0%]; and α-*methyl* β-(2-*hydroxy*-2-*methylpropyl*)*glutarate* δ-*lactone* (XVI) (1·235 g., 51%), b. p. 125·5—126°/0·3 mm., n_D^{21} 1·4622 (Found: C, 59·4; H, 7·8; OMe, 15·2. $C_9H_{13}O_3{\cdot}OMe$ requires C, 60·0; H, 8·05; OMe, 15·5%).

Methyl β-(2-*Chloro*-2-*methylpropyl*)-αα′-*dimethoxycarbonylglutarate* (XII).—Hydrogen chloride (2·5 g., 0·0686 mole) was dissolved in a solution of 16·35 g. of Michael product (X) (0·0495 mole) in dry carbon tetrachloride (50 ml.) at 0°. The solution was set aside for 24 hr. at 0° and for 36 hr. more at room temperature. On removal of the solvent at reduced pressure, the solid product crystallised slowly. Recrystallisation from benzene–hexane gave the *ester* (XII), m. p. 63—63·5° (Found: Cl, 9·6. $C_{15}H_{23}O_8Cl$ requires Cl, 9·7%). Vacuum-distillation yielded the Michael product (X).

Equilibration of the Chloro-ester (XII) *with Ethyl Sodiopropylmalonate*.—Sodium (1·4 g., 0·061 g.-atom) was dissolved in a solution of ethyl *n*-propylmalonate (12·3 g., 0·061 mole) in xylene (25 ml.). This solution (7·25 ml., containing 0·0095 mole of ethyl sodiopropylmalonate) was added in portions of 12—15 drops to a stirred solution of the chloro-ester (3·485 g., 0·0095 mole) in dry xylene (14 ml.) at 53—55°. Each addition was made only after the solution had returned to neutrality. Next morning a few drops of glacial acetic acid were added to the neutral solution. It was then diluted with xylene (50 ml.) and worked up. The products were ethyl *n*-propylmalonate, the Michael product (X), methyl malonate, and methyl α-methoxycarbonyl-δ-methylsorbate (IX).

Methyl β-(2-*Hydroxy*-2-*methylpropyl*)-αα′-*dimethoxycarbonylglutarate Lactone* (XIV).—Hydrogen bromide (1·7 g., 0·021 mole) was dissolved in an ice-cold solution of Michael product (X) (7·08 g., 0·0214 mole) in carbon tetrachloride (50 ml.). After 40 hr. at room temperature, the solution was freed from solvent at reduced pressure. After 4 days the residual bromo-ester (XIII) deposited a solid, which on recrystallisation from benzene–hexane proved to be the *lactone* (XIV), m. p. 76—77° (1·25 g., 18·5%) [Found: C, 53·2; H, 6·3; OMe, 29·0. $C_{11}H_{11}O_5(OMe)_3$ requires C, 53·2; H, 6·4; OMe, 29·4%].

Treatment of the lactone-ester with hydrogen bromide and methanol gave methyl malonate, methyl α-methoxycarbonyl-δ-methylsorbate (IX), and a small amount of starting material.

Attempted Cyclisation of the Michael Product (X) *with Boron Trifluoride*.—Boron trifluoride was dissolved in an ice-cold ethereal solution of the Michael product. The wine-red solution was stored at 0° for 3 days and worked up. Only unchanged starting material was recovered.

One of the authors (H. W. S.) gratefully acknowledges receipt of a grant-in-aid from the Hynson, Westcott, and Dunning Fund.

THE JOHNS HOPKINS UNIVERSITY,
BALTIMORE 18, MARYLAND, U.S.A.

[*Received, September 28th*, 1953.]

The Reduction of Some Carbonyl Compounds with Sodium Borohydride.

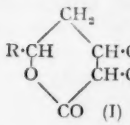
By EVANS B. REID and JOEL R. SIEGEL.

[Reprint Order No. 4683.]

Six carbonyl compounds have been reduced by use of sodium borohydride. Generally it was necessary to use the method of inverse addition in order to obtain reasonable yields of the corresponding alcohols. The latter formed very stable complexes with boron, and were isolated in the pure state after removal of the boron as methyl borate.

THE primary purpose in carrying out the reduction of a series of carbonyl compounds with sodium borohydride was to explore the possibility of utilizing this reaction in a projected synthesis of racemic auxin-a lactone (I; R = 3 : 5-di-*sec*.-butyl*cyclo*pent-1-enyl) (Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181). The literature records

only two syntheses of compounds structurally related to auxin-a. In the first of these, which furnished a model containing the appropriate side chain attached to the unsubstituted *cyclo*pentene ring (Kögl and Ultee, *Rec. Trav. chim.*, 1950, **69**, 1576), the cyclic double bond was incorporated *via* exhaustive methylation. In the second instance (English, Gregory, and Trowbridge, *J. Amer. Chem. Soc.*, 1951, **73**, 615), which resulted in the unsubstituted *cyclo*pentane derivative, the 1 : 2-glycol system was prepared *via* direct hydroxylation of an ethylenic bond. Neither of these approaches is capable of furnishing, in an unambiguous manner, racemic auxin-a lactone.



(I)

A possible approach to the problem would be through selective reduction of the 1 : 2-diketo-lactone corresponding to auxin-a lactone, provided the reaction could be carried out in such a way as to leave untouched both the cyclic double bond and the lactone (or carboxyl) grouping. This specificity was apparently obtained in the use of sodium borohydride by Chaiken and Brown (*ibid.*, 1949, **71**, 122). These authors, however, in describing the use of this reagent in reductions, reported unsuccessful attempts to isolate the reduction products of both glucose and pyruvic acid because of the very stable complexes formed by boron with the polyhydric alcohol and the α-hydroxy-acid, respectively. In dealing with carbohydrates it has since been found possible to eliminate the boron from its complexes by several methods (Abdel-Akher, Hamilton, and Smith, *ibid.*, 1951, **73**, 4691), one of which we have adopted with fair success. This consists in removing the boron as the very volatile methyl borate, by heating the complex with an acidic methanol solution. Under these conditions the α-hydroxy-acids were readily esterified, and this necessitated an additional hydrolysis step. Ester interchange was also found to occur readily.

The application of these procedures to pyruvic acid, glyoxal, mesoxalic acid (in the form of its sodium salt), and phenylglyoxylic acid resulted in satisfactory yields (50—75%) of the corresponding hydroxy-compounds. However, the yields of simple reduction products from both ethyl αβ-dioxobutyrate and ethyl α-acetoxy-β-oxobutyrate were far from satisfactory, *i.e.*, 15—25%.

In dealing with alkali-sensitive compounds (all of the above except mesoxalic acid), it was found necessary to use the method of inverse addition (Bachmann and Dreiding, *ibid.*, 1949, **71**, 3222), in order to minimize undesirable condensations or rearrangements. A typical case was pyruvic acid, affording lactic acid in 61% yield on inverse addition of reductant. On the other hand, when the sodium borohydride solution was added to the pyruvic acid, no lactic acid could be isolated. Instead, a thick syrup was obtained which failed to give tests either for a 1 : 2-glycol or for a ketone, although it did give a positive test for an α-hydroxy-acid when treated with lead dioxide (Baeyer and Liebig, *Ber.*, 1898, **31**, 2106). The substance therefore was not dimethyltartaric acid, earlier obtained by bimolecular reduction of pyruvic acid (Böttinger, *Annalen*, 1877, **188**, 318). It is possible that the reduction product was γ-carboxy-α-hydroxy-γ-valerolactone, formed from para-pyruvic acid (or its lactone) which is known to be formed spontaneously from salts of pyruvic acid (Wolff, *ibid.*, 1899, **305**, 154).

Our work with ethyl αβ-dioxobutyrate met with several unexpected difficulties. For the preparation of this ester in quantity it was found necessary first to form the α-hydroxy-imino-derivative of ethyl acetoacetate according to a revised procedure (E. Coolidge, Diss., The Johns Hopkins Univ., 1949), and to oxidise this derivative with oxides of nitrogen (*Org. Synth.*, John Wiley and Sons, Inc., New York, 1941, Coll. Vol. I, 266). However, the orange-yellow diketone thus obtained formed a colourless crystalline hydrate of m. p. 96—98°. This value, although midway between the m. p.s reported for the hydrates of the methyl and the *iso*propyl ester (80° and 115°, respectively) (Denis, *Amer. Chem. J.*, 1907, **38**, 563), does not agree with either of the values reported for the ethyl ester, *viz.*, 140° (Denis, *loc. cit.*) and 148° (Müller, *Ber.*, 1933, **66**, 1668). It was therefore necessary to prove that our material was authentic diketo-ester, and all the evidence at hand indicates that this is the case. For instance, our product gave the known benzilic acid type of rearrangement to yield *iso*malic acid (Denis, *loc. cit.*); both the hydrate and the free diketo-ester furnished the same dianil, of correct m. p. (Bouveault, *Bull. Soc. chim.*, 1905, **33**, 481); and reduction of both ester and hydrate afforded αβ-dihydroxybutyric

esters. A further unexpected feature was the fact that, even with the method of inverse addition, it was necessary to use massive quantities of reagent to effect complete reduction of the two keto-groups, and this led to much high-boiling product, apparently produced by condensation. Nevertheless, reduction of the ethyl ester gave, after removal of methyl borate, methyl αβ-dihydroxybutyrate in low yield. The same ester was obtained, also in poor yield, by starting with methyl αβ-dioxobutyrate and using sodium borohydride, or in good yield with Raney nickel by the technique of Mozingo, Spencer, and Folkers (*J. Amer. Chem. Soc.*, **1944**, **66**, 1859). It is noteworthy that, while Raney nickel was quite efficient, Adams's catalyst with hydrogen under about 3 atm. pressure was without effect on the dicarbonyl system.

The reduction of either ethyl or methyl α-acetoxy-β-oxobutyrate with sodium borohydride also formed considerable high-boiling material, along with the desired α-acetoxy-β-hydroxy-derivative. As with the αβ-diketo-esters, Adams's catalyst and hydrogen were without action, but Mozingo's technique was quite effective. As a further check on the identity of our reduction products, methyl α-acetoxy-β-hydroxybutyrate, produced *via* Raney nickel reduction, was hydrolysed to the dihydroxy-acid and the latter was esterified, yielding the same methyl dihydroxy-ester as that furnished by sodium borohydride reduction of both the diketo- and the α-acetoxy-β-keto-esters.

Several unsuccessful attempts were made to isolate in crystalline form αβ-dihydroxybutyric acid and its phenylhydrazide. The reason for this lack of success appears to lie in the fact that, although the pure optical forms have been obtained in the solid state, no method has succeeded in separating the two racemic acids, or their derivatives (Braun, *ibid.*, 1929, **51**, 231). It seems safe, therefore, to conclude that sodium borohydride reductions are in no sense stereospecific, and that the product consists of a mixture of the DL-*threo*- and the DL-*erythro*-form.

Experimental

Reduction of Pyruvic Acid.—Freshly prepared pyruvic acid (*Org. Synth.*, Coll. Vol. I, 1941, p. 475) (15·0 g.) was dissolved in water (100 ml.), cooled to 0° and carefully neutralised (final pH 5) with a cold solution of sodium hydroxide (6·85 g.) in water (20 ml.). Portions of this salt solution were then added dropwise (30 min.) to a mechanically stirred solution of sodium borohydride (3·3 g.) in water (35 ml.), the temperature being kept at 10—15°. After storage at 0° for 2½ hr., the mixture was reduced to half-volume under water-pump vacuum, acidified with hydrobromic acid, and again evaporated (reduced pressure) until a thick syrup formed. Excess of 4% methanolic hydrogen bromide (from dry gas) was added to the residue, and methyl borate was removed by gentle warming under reduced pressure (at atmospheric pressure considerable esterification occurred). The crude syrup, freed from sodium bromide, weighed 11·5 g., and gave a negative sodium nitroprusside test for pyruvic acid (Simon, *Compt. rend.*, **1897**, **125**, 534).

The *p*-bromophenacyl ester (Rather and Reid, *J. Amer. Chem. Soc.*, **1919**, **41**, 75), recrystallised from acetone–water, had m. p. 111—113°, not depressed on admixture with authentic material. For the calculation of yield, the sparingly soluble 1-hydroxyethylbenziminazole was prepared (Phillips, *J.*, 1928, 2393) and crystallised from water; it had m. p. 178—180°, not depressed on admixture with authentic substance. On this basis the yield of lactic acid was 61%.

When the reduction was carried out by addition of reductant *to* pyruvic acid, and the product worked up as above, a thick syrup resulted. On attempted purification by distillation obvious decomposition resulted and a thick red-brown fluorescent oil, b. p. *ca.* 175°/15 mm., was obtained. Tests were therefore conducted on the crude product. This was not ketonic, and contained at least one hydroxyl group as shown by a positive test with ceric nitrate reagent (Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, 3rd Edn.), but would form neither a dinitrobenzoate nor a *p*-bromophenacyl ester. On pyrolysis it showed the typical behaviour of an α-hydroxy-acid (Le Sueur, *J.*, 1905, **87**, 1888). The possibility that the compound contained a glycol grouping was eliminated by its negative test with periodic acid (Shriner and Fuson, *loc. cit.*). With lead acetate the compound readily formed a lead salt, but on regeneration from this salt, a solid was obtained that melted over a wide range. After treatment of the syrup with base, followed by acidification, the solution was oxidised with lead dioxide (Baeyer and Liebig, *loc. cit.*), liberating much carbon dioxide. Removal of lead by filtration gave a solution showing a positive iodoform test, and furnishing a very small amount

of a 2 : 4-dinitrophenylhydrazone, m. p. 85—110°. No semicarbazone could be prepared, and no evidence of 1 : 3 : 5-triacetylbenzene (the expected product) could be obtained.

Reduction of Phenylglyoxylic Acid.—The freshly prepared acid (*Org. Synth.*, Coll. Vol. I, 2nd Edn., p. 244, footnote 11, 1941) (5 g.) in water (35 ml.) was neutralised with dilute sodium hydroxide, cooled, and added dropwise (½ hr.) to a vigorously stirred solution of 0·4 g. of sodium borohydride in 10 ml. of water, the temperature of the mixture being kept at 10—18°. On acidification with hydrochloric acid, hydrogen was evolved (from excess of borohydride), and a white solid boron complex (1·2 g.) was precipitated. The filtrate was extracted five times with ether, and the ether was evaporated, leaving 2·2 g. of an organic–boron mixture. Dissolution of the combined solids in benzene–acetone (9 : 1) removed a small amount of mandelic acid, m. p. 118—120°. The insoluble boron-containing residue, m. p. 212—213°, was boiled with 4% methanolic hydrogen chloride until free from boron. The residue was methyl mandelate, m. p. 48—53°. For the isolation of pure mandelic acid it was found best to evaporate the reduction product to dryness under reduced pressure without prior addition of acid. The dry residue was then neutralised with concentrated hydrochloric acid–methanol, excess of 4% methanolic hydrogen chloride added, and the methyl borate removed under reduced pressure until a portion of the solution, when ignited, burned with a pale blue flame. The remainder of the methanol was evaporated, and the residue refluxed with excess of 10% aqueous sodium hydroxide for 1 hr. After acidification the solution was extracted six times with ether (use of a continuous-extraction apparatus occasioned no improvement in yield). Evaporation furnished mandelic acid in 76% yield.

Reduction of Glyoxal.—Commerical 30% glyoxal solution (16·7 g., *i.e.*, 5 g. of glyoxal) was diluted with water (35 ml.), cooled to 0°, and neutralised with dilute sodium hydroxide (final pH 8). This cold solution was then added slowly to a rapidly stirred solution of sodium borohydride (1·7 g.) in water (10 ml.) at such a rate that the internal temperature did not rise above 60°. After acidification, evaporation, and removal of methyl borate as described above, the concentrated mixture was filtered. The sodium chloride was washed with absolute methanol, and the filtrate and washings were combined, neutralised, and distilled, yielding 3·58 g. (72%) of ethylene glycol, b. p. 107—108°/24 mm. The dibenzoate had m. p. 71—73°, undepressed on admixture with authentic material.

Sodium Mesoxalate.—Since in our hands the preparation of crystalline mesoxalic acid (Curtiss, *Amer. Chem. J.*, 1906, **35**, 477) was without success, our reduction experiments were carried out with sodium mesoxalate, prepared as follows. Dibromomalonic acid (Conrad and Reinbach, *Ber.*, 1902, **35**, 1817) (26 g., 0·1 mol.) was refluxed for 3 hr. with sodium hydroxide (18 g., 0·45 equiv.) in water (50 ml.). The sodium mesoxalate was slowly precipitated in 86·4% yield. The dianilino-derivative slowly formed from a concentrated aqueous solution of sodium mesoxalate (0·9 g.) when mixed with concentrated hydrochloric acid (0·6 g.) and aniline (1·8 g.); it (1·9 g.) was washed with alcohol, and had m. p. 118—119·5°. Conrad and Reinbach (*loc. cit.*) report 120°.

Reduction of Sodium Mesoxalate.—To the salt (8 g., 0·054 mol.), dissolved in water (500 ml.) at 60°, was added sodium borohydride (0·55 g., 0·014 mol.) in water (20 ml.), and the solution was rapidly stirred for ½ hr. after mixing was complete. The water was removed (water-pump vacuum), the residue neutralised, and excess of 4% methanolic hydrochloric acid added. After removal of methyl borate, the solution was neutralised, and the remainder of the methanol removed by distillation. Sodium hydroxide was added until the solution contained 10% thereof, the whole refluxed for 2 hr., cooled, and neutralised. Addition of barium chloride (11 g., 0·045 equiv.) in water (25 ml.) precipitated barium tartronate (9 g.). This was washed several times with water, and then shaken for ½ hr. with the stoicheiometric amount of sulphuric acid in fifteen times its volume of water. Evaporation yielded the free tartronic acid in 52·5% yield.

Since the m. p. of tartronic acid is dependent upon the rate of heating (Balk, *Annalen*, 1939, **537**, 286), the diamide was prepared from barium tartronate. The salt (1·06 g.) was mixed with absolute ethanol to a pasty mass, and dry hydrogen chloride was passed through the mixture for 30 min. After standing for 1 hr., the precipitate was removed, and excess of aqueous ammonia was added to the filtrate. The basic filtrate was evaporated the following day, and the residue triturated with 4 ml. of water. The insoluble portion was collected and recrystallised from 2 ml. of hot water containing 0·5 ml. of ethanol. The diamide formed small needles, m. p. 195—196°, undepressed on admixture with authentic tartrondiamide, prepared similarly from barium tartronate, the latter obtained by basic hydrolysis of ethyl monobromomalonate (*Org. Synth.*, Coll. Vol. I, 1941, p. 245).

Ethyl αβ-Dioxobutyrate.—This was best prepared as follows. Ethyl acetoacetate (130 g.,

1 mol.) was mixed with glacial acetic acid (132 ml.) and cooled, and sodium nitrite (74·8 g., 1·08 mol.) in water (180 ml.) was slowly added to the rapidly stirred solution, with the temperature being kept below 10°. The solution was then set aside at room temperature for ½ hr., then extracted several times with ether. The extracts were carefully neutralised with saturated sodium hydrogen carbonate solution, washed with water, dried (Na_2SO_4), and kept cold.

Dry nitrous oxide (*Org. Synth., loc. cit.*) was passed through the dry ethereal solution (ice temperature) for about 5 hr. After several hours at 0°, the mixture was allowed to warm to room temperature and was kept thus for 2 days. The ether was removed under reduced pressure, and the residue cautiously distilled, yielding a fraction, b. p. 79—140°/30 mm. This was dissolved in an equal weight of water, shaken in the cold with excess of calcium carbonate, and extracted fifteen times with ether. The dried extracts ($CaCl_2$) were distilled, yielding 42 g. (30%) of ethyl αβ-dioxobutyrate, b. p. 72—80°/22 mm. The amounts given above are optimum, the yield being severely decreased if larger or smaller amounts of reagents are used.

On exposure to air the product formed the hydrate, m. p. 96—98°. Recorded m. p.s are 140° (Denis, *loc. cit.*) and 148° (Müller, *loc. cit.*). The identity of our product was proved in two ways. The ester hydrate (0·2 g.) was kept in a solution of sodium hydroxide (1·25 g.) in water (5 ml.) for 2 days. After acidification and evaporation under reduced pressure, the residue was extracted with ether. Evaporation of the ether left colourless crystals of *iso*malic acid, m. p. 142° (decomp.), in agreement with Denis (*loc. cit.*). Preparation of the dianil from both ethyl αβ-dioxobutyrate and its hydrate, according to Bouveault (*loc. cit.*), gave crystalline material, m. p. and mixed m. p. 117—118°, in agreement with the reported figure.

Reduction of Ethyl αβ-Dioxobutyrate.—The ester (5 g., 0·0345 mol.) was dissolved in methanol (35 ml.) and added to a rapidly stirred solution of sodium borohydride (4·7 g., 0·011 mol.) in methanol (50 ml.) at such a rate that the temperature was kept at 10—15°. After removal of the methyl borate, the solution was concentrated, refluxed with excess of methanolic hydrochloric acid for 6 additional hours, neutralised, and dried (Na_2SO_4). On distillation a fraction was taken, b. p. 109—112°/10 mm. (yield 18%). The same product was obtained in the same yield starting with the crystalline hydrate of methyl αβ-dioxobutyrate, m. p. 72—74°, obtained in the same manner as the ethyl ester. Reduction gave methyl αβ-dihydroxybutyrate, b. p. 109—112°/10 mm.; Glattfield and Straitiff (*J. Amer. Chem. Soc.*, 1938, **60**, 1385) give b. p. 109°/10 mm. Hydrolysis of the dihydroxy-ester yielded only a thick syrup that could not be induced to crystallise.

Hydrogenation of Methyl αβ-Dioxobutyrate.—A solution of the ester hydrate (9·5 g.) in 300 ml. of absolute ethanol was mixed with 100 g. of freshly prepared Raney nickel (Mozingo, Spencer, and Folkers, *loc. cit.*) and refluxed for 7 hr. After removal of the catalyst by centrifugation, methyl αβ-dihydroxybutyrate was isolated in 52·7% yield.

Reduction of Ethyl α-Acetoxy-β-oxobutyrate.—The acetoxy-ester (8 g., 0·0425 mol.), prepared by Dimroth and Schweizer's method (*Ber.*, 1923, **56**, 1380), was dissolved in methanol (30 ml.) and added with stirring to a solution of sodium borohydride (2·9 g., 0·0764 mol.) in methanol (25 ml.). The temperature of the reaction mixture rose to 55° and then dropped to 31° when the reduction was complete. After neutralisation with methanolic hydrogen chloride, filtration, and concentration, a pale yellow fragrant liquid remained. *Ethyl α-acetoxy-β-hydroxybutyrate* was obtained in about 25% yield, b. p. 98—100°/2 mm. (Found: OC_2H_5, 24·0. $C_8H_{14}O_5$ requires OC_2H_5, 23·7%). The hydroxy-ester gave negative tests for carbonyl groups, and a positive test for hydroxy-groups.

Hydrogenation of Ethyl α-Acetoxy-β-oxobutyrate.—The ester was reduced in 59% yield by the technique described above using Raney nickel. After separation of the catalyst, concentration under vacuum left a thick, green, gelatinous residue, which gave a positive test for nickel with dimethylglyoxime and left a white infusible mass upon ignition. After addition of water to the jelly, it was distilled, and yielded ethyl α-acetoxy-β-hydroxybutyrate without significant decomposition (Found: C, 50·7; H, 7·6. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4%).

One of the authors (J. R. S.) acknowledges with thanks receipt of a grant-in-aid from the Hynson, Westcott, and Dunning Fund.

The Johns Hopkins University,
Baltimore 18, Maryland, U.S.A.

[*Received, September 28th*, 1953.]

Experiments with 5 : 6-*Dihydro*-4-*hydroxy*-6-*phenyl*-2-*pyrone. Part II.* The Basic Hydrolysis of an* α-*Bromo- and an* αα-*Dibromo*-β-*keto*-δ-*lactone.*

By Evans B. Reid and Joel R. Siegel.

[Reprint Order No. 4684.]

Oxidation of 5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone with lead tetra-acetate yielded no clearly defined products. Bromination in a basic medium furnished the 3-bromo-derivative, which exists in two forms. Under hydrolytic conditions the bromo-pyrone appears to undergo a series of consecutive rearrangements, yielding 2-phenylethyltartronic acid; a mechanism is advanced to account for this transformation. The hydroxy-pyrone also forms a crystalline 3 : 3-dibromo-derivative. Attempts to replace the bromine atoms with oxygen were without success, as were efforts to oxidise the parent pyrone directly to the 3 : 4-dioxo-derivative. Evidence is advanced to show that the latter is too unstable for isolation. On reduction, or on hydrolysis, one bromine atom is reduced with the formation of the monobromo-pyrone.

The experiments described in this paper were initiated with a view to developing, on model compounds, procedures that might be applicable to the ultimate synthesis of auxin-a from auxin-b (Kögl, Erxleben, Michaelis, and Visser, *Z. physiol. Chem.*, 1935, **235**, 181). Since sodium borohydride had proved an effective reagent for the reduction of both 1 : 2-dicarbonyl and 1-acetoxy-1-carbonyl compounds (Reid and Siegel, preceding paper), efforts were first directed toward the hydroxylation and/or the acetoxylation of 5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone (I) which is the phenyl analogue of auxin-b in lactone form (Henbest and Jones, *J.*, 1950, 3628; Reid and Ruby, Part I*).

Lead tetra-acetate acetoxylates the methylene group of ethyl acetoacetate (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1380). It readily oxidised the hydroxy-pyrone (I), but the products obtained under various experimental conditions were orange gums that contained lead and slowly hardened in the atmosphere. When they were freed from lead, yellow amorphous inhomogeneous powders remained. These were readily oxidised by Tollens's reagent, and this, together with the absence of a typical colour reaction with sodium nitrite (Wolff, *Annalen*, 1898, **291**, 244; Reid and Ruby, *loc. cit.*) and the formation of a dark precipitate with ferric chloride, indicated that lead tetra-acetate had probably functioned, at least in part, as a dehydrogenating agent (cf. Haworth *et al.*, *J.*, 1935, 635, 643; 1936, 352, 1000; Newman, *J. Amer. Chem. Soc.*, 1940, **62**, 1683) to produce a mixture containing the pyrone (II). Analyses, however, were too erratic to substantiate this conclusion.

In view of the sensitivity of the hydroxy-pyrone to oxidising agents our attention turned to substitution methods, and for these, use of the 3-iodo-pyrone seemed the most desirable. Unfortunately, attempts to iodinate the hydroxy-pyrone were unsuccessful: in hypoiodite solution cleavage occurred, leading to iodoform amongst other products, probably as follows:

(I) ⟶ $Ph{\cdot}CH{:}CH{\cdot}CO{\cdot}CH_2{\cdot}CO_2^-$ ⟶ $Ph{\cdot}CH{:}CH{\cdot}COMe$ ⟶ CHI_3

(cf. Henbest and Jones, and Reid and Ruby, *locc. cit.*). On the other hand, in aqueous-methanolic sodium hydroxide the hydroxy-pyrone smoothly furnished the crystalline, enolic, monobromide (III; R = Br). Proof that the bromine atom was attached to the α-carbon atom was afforded by further bromination to a *non-enolic* dibromopyrone (see below).

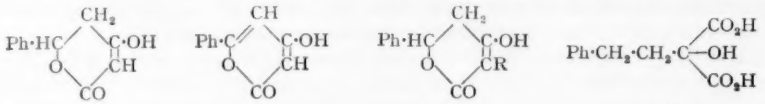
The bromo-pyrone, after repeated recrystallisations from aqueous ethanol, had m. p. 133—134° (decomp.), but exhibited a peculiarity of the hydroxy-pyrone (I) in that its melting point was dependent upon the nature of the solvent used for crystallisation (Reid and Ruby, *loc. cit.*). Thus, after several recrystallisations from benzene, the melting point was 154—155° (decomp.). The compound reverted to the lower-melting form on recrystallisation

* Part I, *J. Amer. Chem. Soc.*, 1951, **73**, 1054.

from hydroxylic solvents. This behaviour is not shown by the enol-ethers or the non-enolic dibromo-derivative of (I). It appeared at first, therefore, that this characteristic was to be attributed to differences in some function, such as hydrogen bonding, for which the enolic hydroxyl group was responsible. However, the infra-red absorption spectra of both forms of the bromo-pyrone were virtually identical and revealed no evidence of hydrogen bonding. The two forms thus appear to be dimorphic modifications, as with the parent hydroxy-pyrone (Reid and Ruby, *loc. cit.*).

Several attempts were made to convert the bromo-pyrone into the acyloin (III; R = OH). With silver oxide suspended in aqueous alcohol no replacement of bromine occurred, the insoluble silver enolate apparently being formed. In hot benzene silver acetate reacted readily, but the product was an intractable gum that appeared to be a decomposition product.

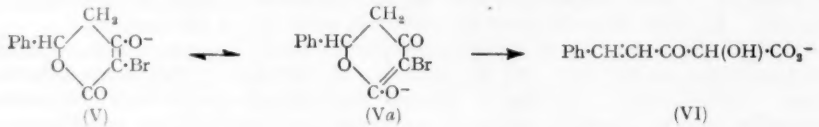
Extended treatment in hot aqueous base removed the bromine atom, furnishing a homogeneous acidic material whose analysis accommodated the structure of the acyloin, but with the incorporation of 1·5 mols. of water. The absence of benzaldehyde amongst the products of oxidation of this substance by potassium permanganate lent credence to the acyloin structure, which was also in harmony with the observation that ceric ion was quickly reduced by the product and by lactic acid. However, titration with the Karl Fischer reagent revealed the empirical formula to be $C_{11}H_{12}O_5,\frac{1}{2}H_2O$, and the facts that the



(I) (II) (III) (IV)

compound failed to respond to 2 : 4-dinitrophenylhydrazine, and in titration showed the presence of two carboxyl groups, definitely eliminated the acyloin possibility.

The presence of a hydroxyl group adjacent to carboxyl was implied by the above-mentioned oxidation by ceric ion, and was substantiated by the observation that in fuming sulphuric acid carbon monoxide was evolved vigorously. That these units were part of a malonic acid grouping was established by decarboxylation, thermally or on acid catalysis, to α-hydroxy-γ-phenylbutyric acid. 3-Bromo-5 : 6-dihydro-4-hydroxy-6-phenyl-2-pyrone (III; R = Br) is thus transformed by basic hydrolysis into a product which, on the basis of the above evidence, can only be 2-phenylethyltartronic acid (IV). In basic solution the bromo-pyrone will exist completely in the anionic form (V ⟷ V*a*); hydrolysis of the bromine atom will therefore not occur without prior or concomitant ring opening (cf.



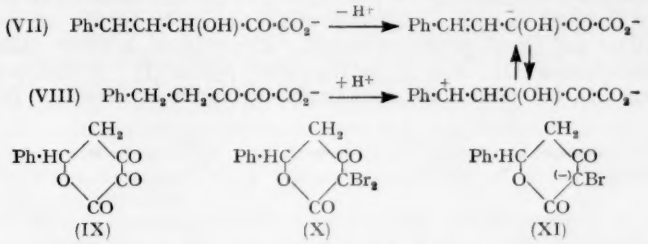
(V) (V*a*) (VI)

ring scission of the parent pyrone type; Jones and Whiting, *J.*, 1949, **1419**, **1423**; Reid and Ruby, *loc. cit.*) resulting in the unsaturated acyloin (VI); this, by a base-catalysed Lobry de Bruyn–van Eckenstein rearrangement, would be expected to equilibrate with the isomeric acyloin (VII), in which $C_{(3)}$ is flanked by two electrophilic groupings so that consequent loss of proton facilitates isomerisation to (VIII); the αβ-diketone (VIII), by the usual benzilic acid rearrangement (cf. Davis *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 3304) would furnish 2-phenylethyltartronic acid (IV), the product isolated.

It should be pointed out that the above mechanism is not entirely without experimental support, for in refluxing base benzylidenelactic acid is known to isomerise to α-oxo-γ-phenylbutyric acid (Petkov, *Annalen*, 1898, **299**, 26).

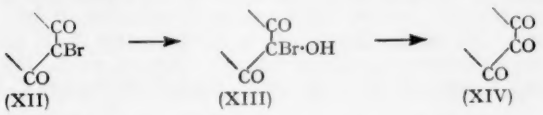
As a possible method for circumventing the above difficulty, and at the same time providing a direct route from the hydroxy-pyrone (I) to the desired 3 : 4-dioxo-pyrone (IX), oxidations with selenium dioxide were explored. This reagent, which oxidises the

methylene hydrogen atoms of ethyl acetoacetate (Müller, *Ber.*, 1933, **66**, 1668), readily attacked the pyrone with formation of the expected intense orange colour. Less than half of the theoretical amount of metallic selenium could be recovered, however, and the product, a deep orange-coloured solid was obviously a complex of selenium, as attested by its colour reaction with thiourea and hydrochloric acid (Lange, " Handbook of Chemistry," Handbook



Publ., Inc., 6th Edn., 1946, Sandusky, Ohio, p. 1137), and by the inability of sulphur dioxide to effect separation (Wattkins and Clark, *Chem. Reviews*, 1945, **36**, 235). In attempts to obtain a pure organic material by reaction with *o*-phenylenediamine, the product, whilst free from selenium, was an amorphous oxygen-sensitive substance that rapidly decomposed on attempted recrystallisation. Although this product appeared to be derived from an α-diketone, this approach had to be abandoned in favour of less direct ones.

Further bromination of the hydroxy-pyrone (I) in a basic medium gave a crystalline dibromo-pyrone (X). The yield was greatly improved by isolation of the intermediate monobromo-pyrone (III; R = Br). The dibromide was non-enolic to ferric chloride solution, and failed to develop colour in the sodium nitrite test, thus affording clear proof of the absence, on the part of both the monobromide and the dibromide, of the $\alpha \longrightarrow \gamma$ rearrangement typical of α-bromoacetoacetic esters (Conrad and Schmidt, *Ber.*, 1896, **29**, 1042; Kharasch, Sternfield, and Mayo, *J. Amer. Chem. Soc.*, 1937, **59**, 1655). Since tests with boiling silver nitrate solutions revealed ready and quantitative removal of *one* bromine atom, experiments were directed toward the formation of the 3 : 4-dioxo-pyrone by metathetical reactions. Use of *either* silver acetate (compare the action of this reagent on ethyl dibromomalonate to yield ethyl mesoxalate and acetyl bromide; Anschutz and Parlato, *Ber.*, 1892, **25**, 3614) *or* silver oxide, gave the expected orange colour characteristic of 1 : 2 diketones, but, as with selenium dioxide oxidation, the products were orange gums that appeared to have undergone partial degradation, yielding cinnamic aldehyde amongst other products. With *o*-phenylenediamine brown powders were obtained that decomposed in air or on attempted recrystallisation. Similar results were obtained upon treating the



dibromo-pyrone itself with *o*-phenylenediamine. The conclusion appeared inescapable that whilst the dioxo-pyrone was probably formed as a primary product it was too unstable to permit isolation (cf. the instability of 3-oxotetronic acid; Michael and Jung, *Ber.*, 1934, **67**, 1660). It thus appeared doubtful whether aqueous hydrolysis, (XII) $\longrightarrow$ (XIV), could be realised, particularly since reductive hydrolysis of the dibromo-grouping would be expected to be a competing reaction. Nevertheless, hydrolysis of the dibromo-pyrone was attempted, first in basic solution, and later in aqueous acetone. The exclusive product, however, was the monobromo-pyrone (III; R = Br), and the reaction gave evidence of formation of hypobromite ion. It has been shown by Altschul and Bartlett (*J. Org. Chem.*, 1940, **5**, 623) that " positivity " of bromine in α-bromo-ketones is dependent on structure and, whilst in some cases negligibly slight, is never entirely absent. On this view, the above

example must be considered a classical one, for the substance is so sensitive to reductive hydrolysis that it is difficult to recrystallise it from hydroxylic solvents without the formation of some monobromo-pyrone. The driving force in this reaction is presumably due to the easy formation of the ion (XI), which, is the electronic equivalent of (V) and (V*a*).

Resonance stabilisation of the bromo-anion, in the sense indicated by (V) and (V*a*), would be eliminated if reduction of the β-oxo-group to the alcohol could be accomplished. The specificity involved in such a reduction would obviously require the use of sodium borohydride (Reid and Siegel, preceding paper). This reagent, however, failed to reduce either the bromo-pyrone (III; R = Br) or the parent pyrone (I). It readily attacked the dibromo-pyrone (X), but yielded the monobromo-derivative exclusively. In this case it

is probable that the reaction was not a hydrolytic reduction, but a true reduction of the carbonyl group, and that the monobromo-pyrone resulted from dehydrohalogenation, as indicated in (XV) ⟶ (XVIII).

Experimental

Oxidation with Lead Tetra-acetate.—The α-form of the hydroxy-pyrone (Reid and Ruby, *loc. cit.*) (5·89 g., 0·0309 mole), in absolute ethyl acetate (400 ml.) was stirred under nitrogen while lead tetra-acetate (13·9 g., 0·031 mole) was added slowly, the temperature being kept below 38°. Ethylene glycol was then added to destroy the excess of tetra-acetate (starch–iodide test), while the mixture was stirred for an additional 15 min. The precipitated lead salts were collected and dissolved in pyridine, and the lead was removed with hydrogen sulphide. The residue was diluted with an equal volume of water, cooled in an ice-bath, and rapidly acidified to pH 2 with dilute hydrochloric acid, causing precipitation of a yellow solid. Evaporation of the ethyl acetate filtrate (above) yielded an orange syrup. This was taken up in pyridine and treated as above, forming the yellow solid in larger amounts (combined yield, 2·50 g.). The product was an intractable mixture: recrystallised from benzene it slowly decomposed at 116—120°; recrystallised from benzene–ligroin it decomposed at 125—135°. The mixed m. p. with original α-pyrone was 105°. The product gave positive tests for the carbonyl group and formed a dark precipitate with ferric chloride solution. With sodium nitrite no colour developed, but positive tests were obtained with both Tollens's and Fehling's solutions. The average of several analyses failed to prove the presence of 4-hydroxy-6-phenyl-2-pyrone (Found: C, 68·4; H, 4·8. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%).

3-Bromo-5-6-dihydro-4-hydroxy-6-phenyl-2-pyrone.—The hydroxy-pyrone (4·74 g., 0·0249 mole) was dissolved in 24·9 ml. of N-sodium hydroxide containing 6 ml. of methanol, cooled below 10°, and rapidly stirred while a solution of bromine (3·98 g., 0·0249 mole) in 29·8 ml. of methanol containing 10 ml. of water was added dropwise. Ice-water (6 ml.) was then added, and the precipitate was collected, washed with ice-water (40 ml.), and air-dried, to give the crude product (5·3 g., 79·3%). On recrystallisation from alcohol–water (2 : 1) colourless needles of the *β-form* of *3-bromo-5-6-dihydro-4-hydroxy-6-phenyl-2-pyrone*, m. p. 133—134° (decomp.), were obtained (Found: C, 49·0; H, 3·4; Br, 29·7. $C_{11}H_9O_3Br$ requires C, 49·1; H, 3·4; Br, 29·7%).

Several recrystallisations from benzene ultimately raised the m. p. to 154—155° (decomp.) (*α-form*) (Found: C, 49·3; H, 3·3; Br, 29·5%).

The α-form was reconverted into the β-form by recrystallisations from aqueous ethanol. Both forms gave intense purple colours with ferric chloride, and with sodium nitrite solution deep pink colours developed in a few minutes. On warming of the bromo-pyrone with a suspension of silver oxide in aqueous ethanol a precipitate containing silver and bromine slowly formed. Ready reaction occurred with silver acetate in hot benzene but gave only gums.

2-Phenylethyltartronic Acid.—The bromo-pyrone (5·86 g., 0·02 mole), dissolved in N-sodium hydroxide (185 ml.), was refluxed for 5 hr., cooled, and extracted with ether. Acidification (hydrochloric acid), extraction with ether (five times), drying (Na_2SO_4), evaporation, and recrystallisation from chloroform or water gave colourless *2-phenylethyltartronic acid*, m. p. 135—137° (decomp.), containing ½ mol. of water of crystallisation (Karl Fischer determination)

(Found : C, 56·9; H, 6·1; H_2O, 3·9. $C_{11}H_{12}O_5,\frac{1}{2}H_2O$ requires C, 56·6; H, 5·6; H_2O, 3·9%) (2·08 g., 47·2%). The compound decolorised ceric nitrate solution, and evolved carbon monoxide vigorously in warm oleum. It was inert to 2 : 4-dinitrophenylhydrazine, and on titration proved to be dibasic.

α-Hydroxy-γ-phenylbutyric Acid.—2-Phenylethyltartronic acid (0·330 g.) was heated under reflux with 9% hydrochloric acid (12 ml.) for 7 hr. and then kept at room temperature for 10 hr. Colourless needles were precipitated. These were washed with ice-water and dried (m. p. 103—105°; 34%) (Found : C, 66·5; H, 6·5. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%). The same product, *α-hydroxy-γ-phenylbutyric acid*, was obtained by heating the tartronic acid at 150° for 25 min. and recrystallising the residue from benzene.

β-Phenylpropaldehyde.—α-Hydroxy-γ-phenylbutyric acid (0·09 g., 0·005 mole), lead peroxide (0·12 g., 0·005 mole), phosphoric acid (0·049 g.), acetic acid (3 g.), and water (5 ml.) were refluxed for 2 hr., and the cooled mixture was filtered with suction. Treatment of the filtrate with 2 : 4-dinitrophenylhydrazine gave β-phenylpropaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 148—150°.

Oxidation of 5 : 6-Dihydro-4-hydroxy-6-phenyl-2-pyrone.—The pyrone (1 g., 0·0053 mole) in hot anhydrous benzene was treated with selenium dioxide (0·59 g., 0·0053 mole). The solution became yellow and then orange. After 3·5 hours' heating, the mixture was filtered, yielding about 40% of the calculated amount of metallic selenium. Evaporation furnished 0·9 g. of an orange selenium-containing solid, soluble in benzene, dioxan, or acetone. Heating this with *o*-phenylenediamine in acetic acid gave a deep red solution which, when poured into water, yielded an orange solid (100 mg.). This gave the purple colour with sulphuric acid characteristic of quinoxaline derivatives (Hickinbottom, " Reactions of Organic Compounds," Longmans Green and Co., London, 1st Edn., 1936, p. 294) and contained no selenium. It rapidly decomposed in air and on attempted crystallisation.

3 : 3-*Dibromo*-5 : 6-*dihydro*-4-*oxo*-6-*phenyl*-2-*pyrone.*—This substance was prepared in one step by treatment of the pyrone in basic solution with two equivs. of bromine, but was best prepared by bromination of the monobromopyrone. The monobromopyrone (6·6 g., 0·025 mole), dissolved in N-sodium hydroxide (24·5 ml.), was cooled below 10° and stirred vigorously while bromine (3·93 g., 0·025 mole), in water–ethanol (20 + 20 ml.), was added dropwise. The precipitated dibromo-pyrone (7·8 g., 85·5%) was washed with water and dried *thoroughly* before recrystallisation. A 72·5% yield of 3 : 3-*dibromo*-5 : 6-*dihydro*-4-*oxo*-6-*phenyl*-2-*pyrone* was obtained as colourless needles, m. p. 114—116°, on recrystallisation from chloroform–hexane (1 : 1) (Found : C, 38·0; H, 2·2; Br, 45·7. $C_{11}H_8O_3Br_2$ requires C, 38·0; H, 2·3; Br, 45·9%).

In *fresh* alcoholic solution the product gave no colour with sodium nitrite solution (Wolff, *loc. cit.*; Reid and Ruby, *loc. cit.*), or dilute ferric chloride. When the dibromo-pyrone (0·2807 g.) in ethanol (50 ml.) containing water (10 ml.) and silver nitrate (0·4 g.) was boiled for 1 hr., 27·8% of the bromine was removed (Calc. : 22·9% for *one* atom).

Reactions with Silver Oxide and Silver Acetate.—The dibromo-pyrone (0·5 g., 0·0014 mole) in anhydrous benzene was heated with silver oxide (0·33 g., 0·0014 mole) until a deep orange colour developed (5·5 hr.). Filtration removed silver bromide and some unchanged oxide, and gave a clear orange solution, which on evaporation yielded an orange gum. Treatment with water failed to lessen the colour and gave no noticeable reaction, although a faint odour of cinnamon was apparent. With *o*-phenylenediamine in acetic acid a tan-coloured solid was formed that blackened in air and on attempted recrystallisation.

With silver acetate (0·24 g., 0·0014 mole) the dibromo-pyrone (0·5 g., 0·0014 mole) in hot anhydrous benzene reacted to yield silver bromide and a deep orange-coloured solution. After 3 hours' heating the product was an orange gum.

Hydrolysis of the Dibromo-pyrone.—(a) *With aqueous base.* The dibromo-pyrone (0·5 g., 0·0014 mole) was heated for 10 min. on the steam-bath with N-sodium hydroxide (20 ml.). Tests for hypobromite ion (starch–iodide) were positive. On dilution and acidification at 0° a small amount of the enolic monobromo-pyrone was precipitated.

(b) *With aqueous acetone.* The dibromo-pyrone (337 mg.) was dissolved in warm acetone–water (30 : 20), and the solution set aside for a day. After removal of the solvent *in vacuo*, the solid residue was crystallised from water–ethanol, yielding the monobromo-pyrone (75 mg., 28·8%), m. p. and mixed m. p. with authentic low-melting form, 132·5—133·5° (decomp.). After four recrystallisations from benzene, the m. p. and mixed m. p. with authentic high-melting form were 153—154° (decomp.).

Reduction of the Dibromo-pyrone.—The dibromo-pyrone (300 mg., 0·0086 mole), dissolved in absolute methanol (10 ml.), was added dropwise to sodium borohydride (0·3 g., 0·003 mole) in

absolute methanol (10 ml.). The reaction was very vigorous. Decomposition of the excess of borohydride with dilute hydrochloric acid precipitated the monobromo-pyrone. After recrystallisation from ethanol–water, the m. p. and mixed m. p. with authentic low-melting form were 132·5—134·5° (decomp.). After several recrystallisations from anhydrous benzene, the m. p. and mixed m. p. with authentic high-melting form were 152·5—153·5° (decomp.). The yield was nearly quantitative.

One of the authors (J. R. S.) acknowledges with thanks receipt of a grant-in-aid from the Hynson, Westcott, and Dunning Fund. In addition the authors thank Dr. Lester P. Kuhn, Ballistic Research Laboratory, Aberdeen Proving Ground, Md., for infra-red absorption spectra.

THE JOHNS HOPKINS UNIVERSITY,
BALTIMORE 18, MARYLAND, U.S.A. [*Received, September 28th*, 1953.]

Tropolones. Part VII. Orientation in Tropolone.*

By J. W. COOK, J. D. LOUDON, and D. K. V. STEEL.

[Reprint Order No. 4751.]

α- and γ-Nitrotropolones and α-bromo-γ-nitrotropolone are prepared and oriented. α- and γ-Aminotropolone and their diazo-reactions are described. α- and γ-Carboxytropolone are prepared, the latter through dehydrogenation of a condensation product of pimelic and oxalic esters. In bromotropolones the replacement of bromine by the *p*-tolylthio-residue is examined.

WITH the establishment of electrophilic substitution in tropolone there is associated the problem of orienting the substitution products. Dewar's prediction on theoretical grounds (*Nature*, 1950, **166**, 790) that γ-substitution would predominate does not provide a complete solution and the practical approach, based on isomerisation of substituted tropolones to derivatives of benzoic acid, sometimes meets with difficulty (cf. Cook and Loudon, *Quart. Reviews*, 1951, **5**, 99). Nitro- and amino-derivatives of tropolone, as of benzene, thus become important as key-compounds for orientation. This is already recognised in substitution studies by Haworth and Hobson on β-methyltropolone (*J.*, 1951, 561) and by Nozoe and his school on hinokitiol [*Proc. Jap. Acad.*, 1950, **26**, (9), 30; 38; 45: 1950, **26**, (10), 25], on methyltropolones [*ibid.*, 1951 **27**, (8), 410; *Sci. Rep. Tôhoku*, 1952, **35**, (4), 242], and on tropolone itself [*Proc. Jap. Acad.*, 1951, **27**, (4), 190; 1951, **27**, (5), 231; *J. Amer. Chem. Soc.*, 1951, **73**, 1895]. Our own study of nitration in tropolone, of which a preliminary account has already appeared (Cook, Loudon, and Steel, *Chem. and Ind.*, 1951, 669), is summarised below together with the results of further search for significant reference compounds.

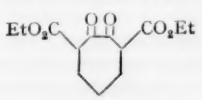
Nitration of tropolone yielded γ-nitrotropolone and a small quantity of α-nitrotropolone. These products were identified by isomerisation, *via* their methyl ethers, to *p*- and *o*-nitrobenzoic acid respectively. Their reduction afforded corresponding aminotropolones of which the γ-isomer is very conveniently also prepared by reduction of γ-*p*-tolylazotropolone. This azo-compound is thereby identified and is the sole product, isolated in high yield, of coupling of tropolone with diazotised *p*-toluidine at pH 6·9. Standard procedures applied to diazotised γ-aminotropolone led to γ-bromo-, γ-cyano-, and γ-hydroxy-tropolone. The amine also underwent Skraup's reaction, affording pyrido(3 : 2-βγ)tropolone (Cook, Loudon, and Steel, *Chem. and Ind.*, 1952, 562). α-Aminotropolone, available in relatively small quantity, is less suited to diazo-reactions since by the action of nitrous acid it is converted, in part at least, into salicylic acid, a type of change which was first observed by Nozoe, Kitahara, and Doi for α-aminohinokitiol (*J. Amer. Chem. Soc.*, 1951, **73**, 1895).

Nitration of α-bromotropolone yielded α-bromo-γ-nitrotropolone (m. p. 138—139°) which was oriented by rearrangement, through its methyl ether, to 2-bromo-4-nitrobenzoic acid. This nitration product differs considerably in m. p. from either of the two bromonitrotropolones (m. p.s 112° and 120°) described, but not rigidly oriented, by Nozoe *et al.* (*Proc. Jap. Acad.*, 1951, **27**, 190, 231).

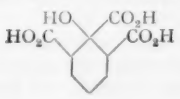
* Part VI, *J.*, 1952, 4416.

Hydrolysis of γ-cyanotropolone afforded γ-carboxytropolone, and this acid served to orient γ-formyltropolone, through the latter's oxidation product, as described in Part VI. The acid was unchanged by sublimation or when heated in pyridine, but was decarboxylated in boiling aniline, tropolone being isolated. It reacted with ethereal diazomethane, forming a methyl ester methyl ether. Hydrogenation of γ-cyanotropolone yielded γ-aminomethyltropolone which was isolated as the picrate.

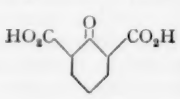
α-Carboxytropolone which was prepared in Part V (*J.*, 1952, 2350), *via* the nitrile, from α-bromotropolone has now been obtained by a method involving synthesis of the tropolone ring. Naumov and Perminova (*Acta Univ. Asiae Mediae*, 1937, [vi], No. 28; briefly abstracted in *Brit. Abs.*, 1940, *A*, II, 48, but otherwise ignored) claim to have prepared 1 : 4-diethoxycarbonyl*cyclo*heptane-2 : 3-dione (I) by condensing pimelic and oxalic esters. Their compound was characterised through reaction products with phenylhydrazine (" phenylhydrazone," m. p. 189—190°) and *o*-phenylenediamine (condensate, m. p. 142°). We obtained by the same route a compound which appears to be identical with this dione and, although its derivatives differ somewhat from those described in the abstract, structure (I) is completely confirmed by its further reactions. For instance, hydrolysis by acid afforded *cyclo*heptane-1 : 2-dione. Alkaline hydrolysis, on the other hand, proceeded with rearrangement to 2-hydroxy*cyclo*hexane-1 : 2 : 3-tricarboxylic acid (II) which was degraded to 2-oxo*cyclo*hexane-1 : 3-dicarboxylic acid (III) and thence to *cyclo*hexanone. When (I) was heated with bromine (2·5 mols.) in acetic acid αα′-dibromo-



(I)



(II)



(III)

tropolone was obtained—probably through bromination–dehydrobromination of *cyclo*heptane-1 : 2-dione formed in the acidic medium. Attempts to dehydrogenate (I) with palladium–charcoal in trichlorobenzene or with chloranil in xylene were unsuccessful, but by the action of iodine in boiling nitrobenzene (cf. Treibs, *Annalen*, 1952, **576**, 110) a product was obtained from which α-carboxytropolone was isolated, albeit in small yield.

Unlike most nucleophilic reagents the salts of thiophenols *exhaustively* replace halogen in *o*-/*p*-polyhalogenonitrobenzenes (Loudon, *J.*, 1940, 1525). In Part V (*loc. cit.*) it was shown that *p*-thiocresol reacts with α-bromotropolone in presence of bases to form α-*p*-tolylthiotropolone. This reagent was therefore tested for its capacity to orient, by replacement, potential anions which are substituents in the tropolone nucleus. Its value, however, appears to be limited. For instance, αα′γ-tribromotropolone by reaction with an excess of *p*-thiocresol in pyridine afforded γ-bromo-αα′-di-*p*-tolylthiotropolone in excellent yield. Nozoe, Satô, and Matsui [*Proc. Jap. Acad.*, 1952, **28**, (8), **407**], who examined the same reaction under rather different conditions, report the simultaneous formation of an isomer which we have not encountered. Our product was identified by its alternative preparation from αα′-dibromotropolone and *p*-thiocresol, followed by bromination of the resultant αα′-di-*p*-tolylthiotropolone. Despite the resistance to replacement thus shown by the γ-bromo-substituent, γ-bromo-αα′-di-*p*-tolylthiotropolone yielded αα′γ-tri-*p*-tolylthiotropolone when heated at 150° in ethanol with the sodium salt of *p*-thiocresol. On the other hand, γ-nitrotropolone was largely recovered from all attempts to replace the nitro- by the *p*-tolylthio-group. This result, and the contrast it provides to the mobility of the nitro-group in *p*-dinitrobenzene, is readily explicable by resonance-stabilisation in the nitrotropolone anion which is present in the basic medium used. Moreover, although isomerisation was not observed with the tropolones examined, the alkalinity of the reagent caused rearrangement to 2 : 3 : 5-trichlorobenzoic acid when 2 : 3 : 5 : 7-tetrachloro*cyclo*heptatrienone was heated with *p*-thiocresol and sodium hydroxide in ethanol. Under similar conditions the toluene-*p*-sulphonate of tropolone afforded 2-*p*-tolylthio*cyclo*heptatrienone (cf. Part V, *loc. cit.*).

Repeated attempts failed to effect *C*-acylation of tropolone or of its methyl ether by the use of perchloric acid in acetic anhydride (Burton and Praill, *J.*, 1950, 2034, and later

papers) or trifluoroacetic anhydride in acetic acid (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1951, 718). From these experiments tropolone was invariably recovered, after hydrolysis where necessary.

Experimental

α- and γ-Nitrotropolone.—(i) A mixture of nitric (0·32 c.c.; *d* 1·42) and acetic (2·9 c.c.) acids was gradually added from a micro-burette to a solution of tropolone (0·6 g.) in acetic acid (10 c.c.). The temperature of the mixture rose to 27° after addition of the first few drops and was kept just below this during subsequent additions. After 12 hr. at room temperature γ-nitrotropolone was filtered off and formed yellow needles (0·16 g.), m. p. 194° (sealed tube), from benzene (Found: C, 50·1; H, 3·0; N, 8·3. Calc. for $C_7H_5O_4N$: C, 50·3; H, 3·0; N, 8·4%). The reaction mother-liquor was diluted with water and continuously extracted with benzene. The recovered solid was fractionally crystallised from benzene, affording first some γ-nitrotropolone (0·16 g.) and then *α-nitrotropolone* (0·08 g.) as yellow prisms, m. p. 153° (from benzene) (Found: C, 50·5; H, 3·2; N, 8·5%). Both isomers give a green colour with ferric chloride in ethanol.

(ii) A similar mixture of products, but in smaller yield, was obtained by mixing solutions of tropolone (0·05 g.) and potassium nitrate (0·048 g.) in concentrated sulphuric acid (1 c.c. each) and, after it had been kept for 12 hr. at room temperature, pouring the orange solution into ice-water.

(iii) A small yield of γ-nitrotropolone was obtained by heating a solution of tropolone (0·1 g.) in water (1·5 c.c.) and nitric acid (0·06 c.c.; *d* 1·42) at 95°, followed by extraction with benzene.

(iv) Nitrogen tetroxide (0·5 g.) in light petroleum (b. p. 60—80°) (5 c.c.) was added with stirring at 10—15° to a solution of tropolone (0·5 g.) in the same solvent (200 c.c.). Stirring was continued for 3 hr., the solvent was decanted, and the residue washed with fresh solvent and then with water. The resultant solid (0·36 g.) afforded mainly γ-nitrotropolone (0·3 g.) and a trace of the α-isomer.

Orientation of α- and γ-Nitrotropolone.—(i) *γ-Nitrotropolone methyl ether* was obtained as bright yellow needles, m. p. 224° (sealed tube) [Nozoe *et al.*, *Proc. Jap. Acad.*, 1951, **27**, (5), 231, give m. p. 232°], from benzene (Found: C, 52·8; H, 3·8; N, 7·9. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%), when solutions of diazomethane in ether and γ-nitrotropolone (0·1 g.) in methanol (10 c.c.) were mixed and, after 12 hr., evaporated. This methyl ether (0·03 g.) was heated under reflux for 3 hr. with sodium methoxide (from 0·02 g. of sodium) in methanol (5 c.c.). 6N-Sodium hydroxide (2 c.c.) was added and, while the methanol was allowed to evaporate, the whole was heated for 1 hr. at 100°. Acidification and recovery from ether afforded *p*-nitrobenzoic acid, m. p. and mixed m. p. 238—239°.

(ii) *α-Nitrotropolone methyl ether*, prepared from α-nitrotropolone and treated as described for its isomer, formed pale yellow crystals, (micro-)m. p. 127°, from ether (Found: C, 53·0; H, 4·1; N, 8·1%) and afforded *o*-nitrobenzoic acid, m. p. and mixed m. p. 136—140°.

α-Bromo-γ-nitrotropolone.—α-Bromotropolone was nitrated at 15—17° by method (i) described under nitration of tropolone. *α-Bromo-γ-nitrotropolone* so produced had m. p. 138—139° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 34·3; H, 1·8; N, 5·9. $C_7H_4O_4NBr$ requires C, 34·2; H, 1·6; N, 5·7%). With diazomethane it afforded a methyl ether (m. p. 196° in sealed tube, but not analytically pure) which, by successive treatment with sodium methoxide in boiling methanol and hydrolysis, yielded 2-bromo-4-nitrobenzoic acid, m. p. and mixed m. p. 159—162°.

γ-p-*Tolylazotropolone.*—Coupling was best effected in a 0·25M-phosphate buffer with pH *ca.* 6·9 (Hitchcock and Taylor, *J. Amer. Chem. Soc.*, 1937, **59**, 1812). Tropolone (0·5 g.) in the buffer solution (60 c.c.) was coupled with 0·1M-toluene-*p*-diazonium chloride in 0·06N-hydrochloric acid. The precipitated *γ-p*-tolylazotropolone (0·9 g.) formed orange crystals, m. p. 201°, from acetone (Found: C, 70·1; H, 5·2; N, 11·8. Calc. for $C_{14}H_{12}O_2N_2$: C, 69·95; H, 5·0; N, 11·7%). The compound of m. p. 190—193° described in Part I (Cook, Gibb, Raphael, and Somerville, *J.*, 1951, 503) was apparently impure.

γ-Aminotropolone.—A 10% solution of sodium dithionite (10 c.c.) was added to γ-nitrotropolone (0·1 g.) in warm water (10 c.c.)—or to *γ-p*-tolylazotropolone (0·36 g.) in acetone (20 c.c.) and water (10 c.c.). The resultant pale yellow solution was neutralised with ammonia, made faintly acid with acetic acid, and exhaustively extracted with ethyl methyl ketone. *γ-Aminotropolone*, recovered from the extract, crystallised as yellow scales, m. p. 173—175°, from xylene (Found: C, 61·4; H, 5·4; N, 10·5. $C_7H_7O_2N$ requires C, 61·3; H, 5·2; N, 10·2%).

α-Aminotropolone, (micro-)m. p. 86° [from light petroleum (b. p. 60—80°)], was obtained by reduction of α-nitrotropolone as described for its isomer (Found: C, 61·5; H, 5·2%). The orange solution obtained by diazotisation in dilute sulphuric acid became red when heated for 30 min. at 100°. Extraction and recovery in ether (charcoal) followed by fractional crystallisation from light petroleum (b. p. 60—80°) afforded (*a*) a more insoluble crystalline substance of (micro-)m. p. 190°, which gave a red-brown colour with ferric chloride in ethanol, but was insufficient in quantity for further characterisation, and (*b*) salicylic acid, (micro-)m. p. 152—155° undepressed by admixture with an authentic sample.

γ-Hydroxytropolone.—γ-Aminotropolone (0·13 g.) in 0·36N-sulphuric acid (8 c.c.) was diazotised at 0° with 7% aqueous sodium nitrite (1 c.c.), and the solution was heated under reflux for 2 hr. γ-Hydroxytropolone was recovered in ether and, after sublimation at 150°/1 mm., formed pale yellow crystals, m. p. (decomp.) 244°, from methanol–benzene (Found: C, 61·1; H, 4·7. Calc. for $C_7H_6O_3$: C, 60·9; H, 4·4%). It gave a deep blue colour with ferric chloride in ethanol. Nozoe *et al.* give m. p. (decomp.) 251° for the same compound when prepared in this way [*Proc. Jap. Acad.*, 1951, **27**, (8), 426], and m. p. (decomp.) 245° when obtained by the action of potassium persulphate on potassium tropolone [*ibid.*, 1952, **28**, (9), 488].

γ-Bromotropolone.—A solution of diazotised γ-aminotropolone, prepared as just described, was added to aqueous cuprous bromide and, after 1 hr. at room temperature, the whole was heated for 1 hr. at 100°. γ-Bromotropolone was obtained by sublimation at 240—260°/1 mm. of the precipitated copper complex and was identified by mixed (micro-)m. p. 186—188° with an authentic specimen (Part III, Cook, Gibb, and Raphael, *J.*, 1951, 2244).

γ-Cyanotropolone.—γ-Aminotropolone (0·32 g.) in 0·72N-sulphuric acid (10 c.c.) at 0° was diazotised with 2% aqueous sodium nitrite (8 c.c.). The cold diazo-solution was stirred into a solution of potassium nickelocyanide and sodium carbonate (cf. Storrie, *J.*, 1937, 1746) and after 12 hr. the mixture was filtered and the filtrate acidified. The resultant precipitate was sublimed up to 200°/0·2 mm. and the sublimate was combined with a small quantity of material recovered in chloroform from the acidified filtrate. *γ-Cyanotropolone* formed yellow needles (0·15 g.), m. p. 236°, from water (Found: C, 65·5; H, 3·4; N, 9·7. $C_8H_5O_2N$ requires C, 65·3; H, 3·4; N, 9·5%). It gave a green-brown colour with ferric chloride in ethanol. When γ-cyanotropolone was treated in alkaline solution with 3% hydrogen peroxide and, after 12 hr., the solution was acidified, an oxidation *product* was obtained as yellow prisms, m. p. (decomp.) 269° (Found: C, 38·1; H, 3·1; N, 8·9. $C_5H_5O_5N$ requires C, 37·8; H, 3·2; N, 8·8%), but was not further investigated.

γ-Carboxytropolone, as yellow needles, m. p. (decomp.) 288°, from acetic acid, was obtained when γ-cyanotropolone was heated with (i) 50% potassium hydroxide for 25 min. (the solution was then acidified), or (ii) concentrated hydrochloric acid for 1 hr. (Found: C, 57·7; H, 3·7. $C_8H_6O_4$ requires C, 57·8; H, 3·6%). It gave a green-brown colour with ferric chloride in ethanol and was decarboxylated when heated with boiling aniline for 1 hr. Tropolone was recovered in ether from the acidified aniline solution and, after sublimation, was identified by mixed m. p. 48—49°. With ethereal diazomethane γ-carboxytropolone afforded the *methyl ester methyl ether* as colourless needles, (micro-)m. p. 184° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 62·1; H, 5·1. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%).

γ-Aminomethyltropolone.—γ-Cyanotropolone (0·05 g.) in ethanol (20 c.c.) containing one molar proportion of hydrogen chloride was hydrogenated (3 hr. for completion) in presence of palladised charcoal (0·025 g.). The brown gum, which was obtained on filtration and evaporation, afforded the *picrate* as brown needles, m. p. (decomp.) 208°, from water (Found: C, 44·3; H, 3·55. $C_{14}H_{12}O_9N_4$ requires C, 44·2; H, 3·2%).

1 : 4-*Diethoxycarbonyl*cyclo*heptane*-2 : 3-*dione* (I).—To a cooled suspension of sodium ethoxide (from 2·18 g. of atomised sodium and 4·4 g. of ethanol) in ether (40 c.c.) ethyl oxalate (7 g.) and then ethyl pimelate (10·3 g.) were slowly added. The resultant solution was heated under reflux for 1 hr., the ether was removed, and the residue heated under distillation conditions at 120—125° for 3 hr. The cooled mass was dissolved in water, and the solution acidified and exhausted with ether. After being washed with aqueous sodium carbonate the ethereal solution was shaken with 8N-sodium hydroxide, and the precipitated yellow salt was collected. Acidification of this salt and recovery in ether gave (I) as colourless prisms, m. p. 70° (from ethanol) (Found: C, 57·7; H, 6·3. Calc. for $C_{13}H_{18}O_6$: C, 57·8; H, 6·6%). It reacted with phenylhydrazine in boiling ethanol to form a *dipyrazolone* which separated as colourless crystals, m. p. (decomp.) 309—311° (Found: C, 70·4; H, 5·1. $C_{21}H_{18}O_2N_4$ requires C, 70·4; H, 5·1%); these crystals when recrystallised from hot acetic acid became purple, without

significant change in m. p. or analytical figures. By heating molar proportions of (I) and *o*-phenylenediamine in ethanol for 1 hr., followed by fractional precipitation through cautious addition of water, two *diazines* were obtained as colourless needles, the less soluble having m. p. 143° (from ethanol) (Found : C, 66·3; H, 6·35; N, 8·1. $C_{19}H_{22}O_4N_2$ requires C, 66·7; H, 6·4; N, 8·2%), and the more soluble, m. p. 84° (from ethanol) (Found : C, 66·7; H, 6·3; N, 8·7%).

The dione (I) resisted hydrolysis by aqueous mineral acid. It was heated under reflux for 2 hr. in a mixture of 25% sulphuric acid and an equal volume of acetic acid. Thereafter the addition of a solution of 2 : 4-dinitrophenylhydrazine in ethanol caused precipitation of a solid which was separated by chromatography (benzene–alumina) into unidentified yellow needles (first eluate), m. p. 142—144° (from ethanol) (Found : C, 51·3; H, 4·8; N, 17·3%), and red needles (later eluates), m. p. 198—200° (from benzene). The latter substance was identified by mixed m. p. as the bis-2 : 4-dinitrophenylhydrazone of *cyclo*heptane-1 : 2-dione containing benzene of crystallisation (Part VI, *loc. cit.*) (Found : C, 53·6; H, 5·0; N, 20·1. Calc. for $C_{19}H_{18}O_8N_8,C_6H_6$: C, 53·2; H, 4·3; N, 19·85%).

2-*Hydroxy*cyclo*hexane*-1 : 2 : 3-*tricarboxylic Acid* (II).—The dione (I) (0·1 g.) was heated under reflux with 6N-sodium hydroxide (5 c.c.) for 15 min. during which the precipitated yellow salt became colourless. Acidification and recovery in ether afforded a gum which slowly solidified, forming 2-*hydroxy*cyclo*hexane*-1 : 2 : 3-*tricarboxylic acid* as colourless needles, m. p. (decomp.) 215—216° (sealed tube) from ethyl acetate (Found : C, 46·0; H, 4·8; equiv., 79·7. $C_9H_{12}O_7$ requires C, 46·55; H, 5·2%; equiv., 77·3).

2-*Oxo*cyclo*hexane*-1 : 3-*dicarboxylic Acid* (III).—Compound (II) dissolved with effervescence in cold concentrated sulphuric acid. After 12 hr. the solution was poured into ice, affording the 1 : 3-*dicarboxylic acid* as needles (from water) which melted with decomposition over a range from *ca.* 120° to 140° (Found : C, 51·8; H, 5·6. $C_8H_{10}O_5$ requires C, 51·6; H, 5·4%). [The diethyl ester of this acid is described by Guha and Seshadriengar (*Ber.*, 1936, **69**, 1207).] When warmed with Brady's reagent the acid gave *cyclo*hexanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 156—158°.

αα′-*Dibromotropolone*.—A solution of (I) (1·4 g.) in acetic acid (20 c.c.) containing bromine (2 g.) was heated under reflux for 5 hr. The residue obtained by evaporation *in vacuo* was dissolved in ether, and the solution shaken with strong aqueous sodium hydroxide. The resultant yellow precipitate when dissolved in water and acidified afforded αα′-dibromotropolone as colourless needles (0·4 g.), m. p. and mixed m. p. 156° (from methanol) (Part III, *loc. cit.*).

α-*Carboxytropolone*.—A solution of (I) (1 g.) in nitrobenzene (5 c.c.) containing a small crystal of iodine was heated under reflux for 30 min. Sufficient 6N-sodium hydroxide was added to the cooled solution to maintain slight alkalinity, and the nitrobenzene was removed in steam. The residual liquor was acidified and extracted first with ether and then with ethyl methyl ketone. The brown mass recovered from the ethereal extract was sublimed up to 160°/20 mm., affording a carboxylic acid as needles (0·5 g.), m. p. 128—130° [from benzene–light petroleum (b. p. 60—80°)] (Found : C, 54·0; H, 6·6%; equiv., 285. $C_{13}H_{20}O_7$ requires C, 54·15; H, 7·0%; equiv., 288). This acid, which did not produce colour with ferric chloride in ethanol, dissolved with effervescence in aqueous sodium hydrogen carbonate and in warm concentrated sulphuric acid. It is regarded as *diethyl* 2-*carboxy*-2-*hydroxy*cyclo*hexane*-1 : 3-*dicarboxylate*, probably formed from unchanged (I) during working up. From the ethyl methyl ketone extract a yellow mass was recovered and sublimed at 100—120°/2 mm., affording α-carboxytropolone (0·01 g.), m. p. and mixed m. p. 202° (decomp.), with the sample described in Part V (Found : C, 57·65; H, 4·0. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·6%) : it gave a green-brown colour with ferric chloride in ethanol.

γ-*Bromo*-αα′-*di*-p-*tolylthiotropolone*.—(i) αα′γ-Tribromotropolone (0·2 g.) and *p*-thiocresol (0·21 g.) were heated under reflux with pyridine (5 c.c.) for 1 hr., both in presence and in absence of sodium hydroxide (0·067 g.). In each case the precipitate obtained on acidification afforded γ-bromo-αα′-di-*p*-tolylthiotropolone as yellow prisms, m. p. 216°, from acetic acid (Found : C, 56·2; H, 3·9. Calc. for $C_{21}H_{17}O_2BrS_2$: C, 56·6; H, 3·85%). (ii) The same compound, m. p. and mixed m. p. 214—216°, was obtained when αα′-di-*p*-tolylthiotropolone (0·05 g.) [Nozoe *et al.*, *Proc. Jap. Acad.*, 1952, **28**, (8), 410] was heated with bromine (0·025 g.) in acetic acid (2 c.c.) for 1 hr.

αα′γ-*Tri*-p-*tolylthiotropolone*, m. p. 182° (from acetic acid), was obtained when γ-bromo-αα′-di-*p*-tolylthiotropolone (0·26 g.), *p*-thiocresol (0·06 g.), and sodium hydroxide (0·026 g.) were heated in ethanol (5 c.c.) at 150° for 12 hr. and the whole was added to dilute sulphuric acid (Found : C, 69·1; H, 5·0. $C_{28}H_{24}O_2S_3$ requires C, 68·8; H, 4·95%). It gave an orange-brown colour with ferric chloride in ethanol.

2-p-*Tolylthio*cyclo*heptatrienone*, m. p. and mixed m. p. 147—148° [from benzene–light petroleum (b. p. 60—80°)], was obtained when tropolone toluene-*p*-sulphonate (0·09 g.) (Doering and Hiskey, *J. Amer. Chem. Soc.*, 1952, **74**, 5688), *p*-thiocresol (0·04 g.), and sodium hydroxide (0·013 g.) were heated in ethanol for 1 hr. and the solution was then concentrated and poured into water.

Under similar conditions 2 : 3 : 5 : 7-tetrachloro*cyclo*heptatrienone (Doering and Knox, *ibid.*, p. 5683) afforded 2 : 3 : 5-trichlorobenzoic acid which was recovered in ether from the acidified concentrates and had m. p. and mixed m. p. 166°.

One of us (D. K. V. S.) gratefully acknowledges a Maintenance Allowance from the Department of Scientific and Industrial Research.

THE UNIVERSITY, GLASGOW, W.2. [*Received, October 26th*, 1953.]

The Influence of Uranyl and Thorium Salts on the Miscibility of Phenol and Water.

By S. T. BOWDEN and J. H. PURNELL.

[Reprint Order No. 4629.]

The critical solution temperature (C.S.T.) of phenol and water is depressed by uranyl acetate but raised by uranyl nitrate or sulphate and by thorium nitrate or sulphate. At certain concentrations precipitation of a basic sulphate occurs in the systems containing thorium sulphate. For the other systems a logarithmic relation exists between the concentration of the salt and the depression or elevation of the C.S.T. The depression constant is 0·96 and the elevation constant is 0·86, which is identical with that found for systems containing salts of the light metals. In the lyotropic series representing the influence of ions on the C.S.T. of phenol and water, UO_2^{2+} lies between Be^{2+} and Pb^{2+}, while Th^{4+} falls between K^+ and NH_4^+.

THE influence of uranyl acetate, nitrate, and sulphate, and of thorium nitrate and sulphate on the miscibility of phenol and water has been examined in order to ascertain the relation between concentration and the change in C.S.T., and to establish on this basis the position of UO_2^{2+} and Th^{4+} in the lyotropic series.

EXPERIMENTAL

Purification of Materials.—Water was freed from grease by distillation in an all-glass apparatus. Phenol was purified by repeated distillation in an apparatus provided with a guard tube ($CaCl_2$) until it had m. p. 40·75°. Uranyl nitrate hexahydrate was twice crystallised from dilute nitric acid; gravimetric determination of the uranium content showed that the salt was 99·97% pure. Uranyl sulphate trihydrate was thrice crystallised from dilute sulphuric acid, and was 99·95% pure. Uranyl acetate dihydrate was recrystallised from dilute acetic acid, and had a purity of 99·93%.

Commercial thorium sulphate, after two crystallisations from dilute sulphuric acid in a desiccator over concentrated sulphuric acid, gave a product corresponding to the nonahydrate. Owing to the low solubility of the substance in the liquids under study, it was dehydrated by heating it at 360° for 1 hr. The anhydrous thorium sulphate thus obtained had a purity of 99·69%. Thorium nitrate hexahydrate was obtained by crystallisation of the commercial hydrate from dilute nitric acid in a desiccator containing sulphuric acid. The largest crop of crystals consisted of hexahydrate of purity 99·56%.

Determination of Miscibility Points.—A known weight of phenol was placed in a constricted, thin-walled test-tube, and a pre-determined volume of water or of a standard aqueous solution of the third component was introduced by means of a pipette. After being weighed, the tube was hermetically sealed to prevent evaporation losses.

The miscibility tube, which was fixed by a spring clip to the extended armature of an electric buzzer in series with a switch and 6-v battery, was completely immersed in the water contained

in a 2-l. beaker, and could be brought into rapid oscillation by closing the circuit. This arrangement served not only to agitate the contents of the miscibility tube but also to stir the heating bath and thus ensure rapid thermal equilibration. The bath was heated by a micro-burner, and

TABLE 1. *Phenol and water.*

Phenol, %	9·93	12·53	15·02	17·89	20·00	24·76	31·86	35·21	40·52
t	34·00°	51·90°	55·90°	61·70°	63·20°	65·40°	65·55°	65·65°	65·50°
Phenol, %	45·66	49·64	55·09	60·75	62·48	65·29	67·31	70·84	
t	65·20°	63·20°	59·55°	52·60°	48·50°	42·85°	36·20°	23·80°	

TABLE 2. *Phenol, water, and specified third component.*

PhOH, %		PhOH, %	*t*	PhOH, %	*t*	PhOH, %	*t*	PhOH, %	
Uranyl acetate									
m = 0·01945		m = 0·03441		m = 0·05822		m = 0·09872		m = 0·14730	
10·33	38·5°	10·25	40·6°	14·61	53·0°	15·00	51·2°	15·01	48·3°
20·46	61·6	19·90	60·4	19·16	58·2	19·62	55·6	20·95	52·1
30·92	64·1	25·53	62·1	24·27	60·4	24·25	57·5	24·18	54·0
35·58	64·3	30·14	63·1	29·55	61·3	29·52	58·3	29·20	54·9
42·55	64·2	34·71	63·3	34·93	61·6	34·69	58·8	34·67	55·7
50·93	61·5	40·00	63·3	39·69	61·6	39·89	59·0	39·08	56·0
59·60	52·7	49·52	61·1	48·04	59·6	49·84	56·9	49·64	53·8
		50·12	60·9	56·69	48·3	59·68	45·8		
Uranyl nitrate									
m = 0·01800		m = 0·02982		m = 0·05122		m = 0·07900		m = 0·16981	
14·67	59·7	14·67	62·3	17·19	65·3	16·28	66·9	16·50	73·3
20·07	65·3	20·50	66·3	22·37	68·9	21·68	71·4	22·12	77·5
24·72	67·2	24·30	68·3	30·86	70·8	30·17	73·0	29·23	79·5
29·86	68·0	29·41	69·3	36·55	71·3	35·30	73·6	34·25	80·6
34·83	67·9	33·82	69·4	41·00	71·5	39·36	74·2	39·79	81·8
39·97	68·0	39·20	69·4	45·25	71·4	45·06	73·6	44·32	82·6
45·10	67·5	45·35	69·2	50·41	70·5	50·40	74·2	49·23	83·3
50·52	66·2	50·11	68·2	60·07	63·9	60·05	69·4	59·43	81·2
59·59	58·6	59·09	60·2						
Uranyl sulphate									
m = 0·01126		m = 0·02482		m = 0·04643		m = 0·07597		m = 0·12210	
12·30	58·4	12·17	56·1	12·17	58·5	12·07	59·4	17·17	72·1
18·40	62·8	17·40	63·4	17·96	65·9	17·91	67·7	24·37	78·6
24·94	67·3	23·45	67·6	25·08	70·6	24·60	73·1	29·32	80·3
30·11	68·2	29·62	69·4	29·07	71·7	29·53	74·2	34·91	84·0
34·90	67·9	35·45	69·9	35·45	73·1	34·28	75·7	39·34	87·2
40·29	68·0	40·27	70·4	39·78	74·2	40·02	77·7	45·20	95·4
50·37	67·5	50·22	81·5	49·91	77·6	45·57	80·4	49·92	100·00
59·57	59·2	60·40	71·4	59·00	85·0	50·57	84·9		
						60·51	100·0		
Thorium nitrate									
m = 0·02081		m = 0·04736		m = 0·06015		m = 0·10845		m = 0·14341	
12·44	54·7	9·51	42·4	12·23	61·4	12·38	62·4	10·00	57·0
17·77	66·4	17·38	68·2	18·18	71·0	17·15	73·7	12·17	70·4
25·11	70·0	24·67	71·7	30·05	76·0	24·34	79·4	17·84	79·5
30·01	70·4	29·74	73·1	35·77	77·1	28·76	81·2	24·39	84·5
34·95	70·6	34·82	73·5	40·33	77·8	33·88	82·6	29·30	86·4
39·88	70·9	39·57	74·2	49·79	79·4	39·49	83·9	34·11	88·0
50·39	69·9	42·35	74·4	58·81	76·7	50·13	87·2	39·75	90·3
59·61	63·5	49·79	74·2			59·53	89·2	43·70	92·0
								47·95	93·5
Thorium sulphate									
m = 0·00371		m = 0·00665		m = 0·00798		m = 0·01565		m = 0·02281	
9·89	41·6	12·33	53·5	12·52	53·2	17·35	63·3	12·60	54·9
14·45	60·2	17·48	62·4	17·62	62·7	19·97	65·6	17·43	64·8
20·02	64·3	25·17	66·7	24·99	67·3	24·86	68·0	19·89	66·8
24·94	66·5	30·29	67·5	30·32	67·9	29·83	68·7	24·89	68·9
29·90	66·7	35·17	67·8	34·91	68·2	34·54	69·0	29·81	69·4
35·09	67·3	40·42	67·7	39·93	68·4	37·75	69·4	34·88	69·8
40·62	67·3	50·29	66·1	50·33	66·5 *	39·88	69·4 *	39·77	70·4 *
49·46	65·3	60·16	58·0	59·64	59·7 *	44·60	69·6 *	44·51	70·6 *

* In these systems there was precipitation of a basic sulphate at the compositions indicated.

the temperature was registered by a calibrated thermometer with its bulb set in the vicinity of the miscibillity tube. The system was heated to a temperature 4—5° above the clearing point, and then allowed to cool at a rate of about 0·5°/min. The temperature at which the system became turbid was taken as the miscibility temperature, since the development of turbidity was rapid and more readily observed than the reverse change to homogeneous solution. Each value recorded is the mean of at least three determinations.

Mixtures covering the range 10—70% of phenol were examined in this way, and the results for the binary system are recorded in Table 1, where t is the miscibility temperature. The C.S.T. is 65·65—65·70° and the critical solution composition corresponds to 38·4% of phenol; these values agree closely with those obtained by Hill and Malisoff (*J. Amer. Chem. Soc.*, 1926, **48**, 918) and McKinney (*Trans. Roy. Soc. Canada*, 1927, iii, **21**, III, 256). In common with the majority of mutual solubility curves for mixtures of organic compounds, the curve for phenol and water has a flat maximum (Woodburn, Smith, and Tetewsky, *Ind. Eng. Chem.*, 1944, **36**, 588), owing to the conditions obtaining in the system when the interfacial tension between the solution and the molecular clusters vanished (Rice, *J. Chem. Phys.*, 1947, **15**, 314; *Chem. Reviews*, 1949, **44**, 69). In this region we found that the change from homogeneity to heterogeneity was sharp, but the miscibility temperatures corresponding to the steep parts of the curve were not so readily ascertained in view of the fact that the change was much more gradual. Strong opalescence was observed at all compositions in the neighbourhood of the critical point, and this persisted in the presence of high concentrations of the various third components.

The miscibility data for the ternary systems are listed in Table 2, where m is the molality with reference to the aqueous solution.

Discussion

In accordance with the Timmermans's rules, salts generally cause an elevation of the C.S.T. when one of the components of the binary mixture is water. Among the exceptions for the phenol–water system is sodium acetate, and we find a similar behaviour with uranyl acetate.

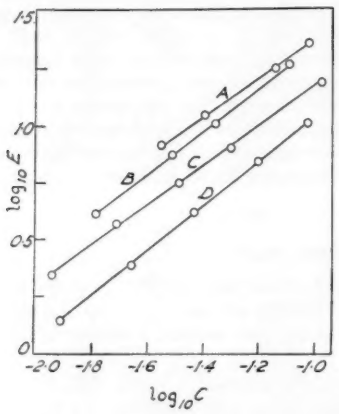
According to Carrington, Hickson, and Patterson (*J.*, 1925, **127**, 2544) the elevation or depression for concentrations greater than about 0·01 mole per 1000 g. of the mixture for systems which do not undergo hydrolysis or form complexes in solution is related to the concentration by the equation $e = aC^b$, where a is a constant characteristic of the third component and b is a constant characteristic of the binary system. The data obtained in the present work are listed in Table 3, where C is the concentration in moles of third component per 1000 g. of the ternary mixture, t_0 is the corresponding C.S.T., e is the elevation in °C, and E is the molecular elevation.

Table 3. *Elevation of C.S.T.*

C	t_0	e	E	C	t_0	e	E	C	t_0	e	E
Uranyl acetate				Uranyl nitrate				Uranyl sulphate			
0·01258	64·3°	1·40°	−111·3°	0·01165	67·9°	2·20°	188·8°	0·00751	68·2°	2·50°	333·3°
0·02219	63·3	2·40	−108·2	0·01924	69·4	3·70	192·3	0·01655	70·0	4·25	257·0
0·03730	61·6	4·10	−109·9	0·03288	71·2	5·55	168·8	0·03095	73·0	7·30	235·8
0·06261	58·8	6·85	−109·4	0·05032	73·6	7·90	157·0	0·04398	75·6	9·90	225·0
0·09234	55·7	10·00	−108·3	0·10580	80·7	15·05	142·2	0·08140	85·9	18·20	223·6
Thorium nitrate				Thorium sulphate							
0·01386	70·7	5·00	360·4	0·00241	67·3	1·65	684·8				
0·02824	73·8	8·10	287·0	0·00432	67·8	2·15	497·5				
0·04010	77·3	11·60	289·3	0·00519	68·2	2·50	481·7				
0·07230	83·0	17·30	236·5	0·01017	69·1	3·40	334·2				
0·09561	88·0	22·30	233·2	0·01482	69·8	4·15	280·0				

Ionisation of uranyl salts in water is accompanied by formation of complex ions which undergo constitutional changes with dilution (Dittrich, *Z. physikal. Chem.*, 1899, **29**, 465; Gomez, *Anal. Fís. Quím.*, 1919, **17**, 24; Guiter, *Bull. Soc. chim.*, 1947, **14**, 64), and the behaviour of the salts in hydroxylic organic solvents is considered to be due either to direct co-ordination of the solvent molecule to the central atom or to hydrogen bonding between the solvent molecule and the water of hydration (Glueckauf, McKay, and

Mathieson, *Trans. Faraday Soc.*, 1951, **48**, 438). However, as shown in the Figure, the plots of log e against log C for the systems containing uranyl salts (the sign of the elevation for the acetate being ignored) are straight lines, and it is evident, therefore, that Patterson's equation is obeyed by these systems. The values of the constants are as follows: uranyl acetate, $a = -99{\cdot}5$, $b = 0{\cdot}96$; uranyl nitrate, $a = 101{\cdot}0$, $b = 0{\cdot}85$; uranyl sulphate, $a = 163{\cdot}3$, $b = 0{\cdot}89$; thorium nitrate, $a = 178{\cdot}6$, $b = 0{\cdot}85$. As found by previous workers, the binary system constant varies according as there is elevation or depression of the C.S.T., but the average value of b for systems exhibiting elevation (0·86) agrees with that found (0·87) by Carrington *et al.* (*loc. cit.*). For the systems containing uranyl salts the values of a furnish further confirmation of the rule that sulphates produce greater elevation than the corresponding nitrates. The system containing thorium nitrate also



A, Thorium nitrate.
B, Uranyl sulphate.
C, Uranyl nitrate.
D, Uranyl acetate.

conforms to Patterson's equation despite the fact that complexes are formed through co-ordination of the thorium with the oxygen atoms of the solvent molecule (Templeton, Rothschild, and Hall, *J. Phys. Coll. Chem.*, 1949, **53**, 838). The linear relation is not obeyed by the thorium sulphate system, but this behaviour is to be expected inasmuch as the concentrations lie outside the range to which Patterson's rule is applicable.

The influence of a series of ions on the C.S.T. of a binary system is similar to that shown by the Hofmeister series in the coagulation of neutral egg albumin. The positions of the uranyl and thorium ions in the series may be ascertained by comparing the elevations of the C.S.T. with the values found for other salts at corresponding concentrations (Duckett and Patterson, *J. Phys. Chem.*, 1925, **29**, 295); this places the uranyl ion between the beryllium and lead ions, and the thorium ion between the alkali-metal and ammonium ions.

The effects of the alkali-metal ions and of the ammonium and hydrogen ions on the C.S.T. of phenol and water are in the reverse order of those found by Briggs (*ibid.*, 1928, **32**, 1646) for the change in zeta potential at the cellulose–water interface. It is evident from the present work also that there is a reversal of order with respect to the effects of the thorium and alkali-metal ions, and that the thorium ion has a greater effect than the ammonium and hydrogen ions on the C.S.T.

TATEM LABORATORIES, UNIVERSITY COLLEGE, CARDIFF. [*Received, September 4th*, 1953.]

Miscibility Phenomena in Ternary Systems containing Diphenyl Ether, Water, and an Aliphatic Alcohol or Acid.

By J. H. Purnell and S. T. Bowden.

[Reprint Order No. 4630.]

Binodal curves and tie-lines of eight systems have been determined in order to ascertain the influence of alcohols and fatty acids on the miscibility of diphenyl ether and water. For a series of homologous third components there is no simple relation between the composition of the critical mixture and the position of the component in the series, but for systems containing the straight-chain alcohols the concentrations corresponding to the summits of the binodal curves are linearly related to the number of carbon atoms in the molecule. The observed equilibria do not conform to Bancroft's equation over the entire range of composition. The system containing *n*-propanol exhibits solutropism (see p. 544) involving reversal of slope of the tie-lines.

The hypothesis that tie-lines for non-solutropic systems meet at a point focus is not substantiated by the results of the present work. A study of the methods of tie-line correlation reveals that they are not generally applicable and that the method proposed by Othmer and Tobias is the most satisfactory.

Apart from the studies of Washburn, Graham, Arnold, and Transue (*J. Amer. Chem. Soc.*, 1940, **62**, 1454), there have been no systematic investigations of the relation between the molecular structure of a liquid and its solvent power for a pair of immiscible or partially miscible liquids. The behaviour of water and diphenyl ether in the presence of an aliphatic alcohol or acid has now been studied primarily in order (*a*) to ascertain whether there is any relation between homology and the composition of the critical mixture or that corresponding to the summit of the binodal curve, (*b*) to examine the applicability of Bancroft's distribution equation, (*c*) to test the hypothesis that tie-lines of non-solutropic systems meet at a point focus, and (*d*) to assess the accuracy of the various methods of tie-line correlation.

Experimental

Weights were standardised by Richards's method, and thermometers were tested against Anschutz thermometers calibrated at the N.P.L. Unless otherwise stated, b. p.s refer to 760 mm. pressure. Densities were corrected for buoyancy, and refractive indices were determined by means of an Abbé refractometer with its prisms kept at constant temperature by a stream of water from a thermostat.

Purification of Materials.—Diphenyl ether. Repeated fractional distillation of the commercial ether gave a product with b. p. 258·4°, f. p. 26·9°, n_D^{27} 1·5780.

Alcohols. The alcohols were dried by partial conversion into the magnesium alkoxide (Lund and Bjerrum, *Ber.*, 1931, **64**, 210), and were then fractionated through a Dufton all-glass column in a distillation apparatus provided with a guard-tube ($CaCl_2$): methanol, b. p. 64·6°, D_4^{25} 0·78665, n_D^{25} 1·3272; ethanol, b. p. 78·4°, d_4^{25} 0·78504, n_D^{25} 1·3596; *n*-propanol, b. p. 97·2°, d_4^{25} 0·79988, n_D^{25} 1·3840; *iso*propanol, b. p. 82·1°, d_4^{25} 0·78088, n_D^{25} 1·3764; butanol, b. p. 117·7°, d_4^{25} 0·80574, n_D^{25} 1·3970.

Acids. Fractional freezing of acetic acid followed by distillation gave a product with f. p. 16·6°, b. p. 118·1°, d_4^{25} 1·04367, n_D^{25} 1·3698.

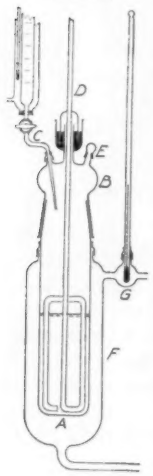
The other acids were purified by distillation: propionic acid, b. p. 141·3°, d_4^{25} 0·98842, n_D^{25} 1·3848; butyric acid, b. p. 164·0°, d_4^{25} 0·95091, n_D^{25} 1·3958.

Miscibility Apparatus.—The miscibility vessel (Fig. 1) consisted of the flat-bottomed Pyrex tube *A* (20 cm. long and 4 cm. in diameter) with a ground joint at its upper end for fitting into the cap *B*, which was provided with three collars to take the delivery tube of the burette *C*, the mercury-sealed stirrer *D*, and the ground-glass cap *E*, respectively. The burette (10 ml.) was furnished with a glass jacket through which water at 25·0° was circulated, and the upper end of the burette was fitted with a guard-tube ($CaCl_2$) to maintain a dry atmosphere above the organic liquid during its introduction into the miscibility vessel. The stirrer *D* was driven by an electric motor at a rate of about 300 r.p.m., so that thorough agitation of the liquid was effected without

splashing. The ground-glass joints of the apparatus were lubricated with Apiezon L grease to prevent intrusion of atmospheric moisture.

Owing to the peculiar optical effects accompanying the phase changes in the systems under study, it proved extremely difficult to observe the clearing and turbidity points when the miscibility vessel was immersed in the water of an ordinary thermostat. This difficulty was largely overcome by surrounding the miscibility vessel with the glass jacket *F* (25 cm. long and 6·5 cm. in diameter) through which water from a thermostat was circulated at high speed by means of a rotary pump driven by an electric motor. The exit tube of the jacket was provided with the small reservoir *G* to accommodate the bulb of a thermometer. The thermostat was kept at 25° ± 0·05° by means of a bimetallic element operating a vacuum switch relay in circuit with an immersion heater. The speed at which the water was circulated through the jacket was such that the temperature of the issuing stream did not differ by more than 0·05° from that of the thermostat.

FIG. 1.



Determination of Binodal Curves.—The binodal curve of a system was generally determined in three stages. In the first diphenyl ether (about 6 g.) and water (about 0·05 ml.) were introduced into the miscibility vessel, and the mixture was stirred until thermal equilibrium was attained (20—30 min.). The third component was then added dropwise from the burette until the mixture formed a homogeneous solution. The addition was made very slowly in the neighbourhood of the miscibility point, and the stirring was momentarily interrupted when it was necessary to observe the state of the system. Normally, determination of a miscibility point occupied 30—45 min. The weights of water and third component in the system were calculated from the known values of the densities.

Small samples of the solution were withdrawn for refractometric analysis by the use of a long capillary tube with a small bulb (0·5 ml.) at one end. The bulb was warmed, the cap *E* removed, and the capillary tube inserted into the miscibility vessel so that its open end was immersed in the solution. After a sufficient amount of the liquid had been drawn into the capillary, the sampler was removed and allowed to cool further so that the liquid was drawn into the bulb. The sampler was then sealed by directing a small flame at a point about 2 cm. from the open end. After cooling to room temperature, it was weighed, and from a knowledge of the composition of the mixture, allowance was made for the amount of each component withdrawn from the miscibility vessel. Further quantities of water were added to the mixture, and the miscibility points were determined for the range 70—15% of diphenyl ether.

In the second stage about 1 g. of diphenyl ether was employed to cover the range 50—5%, and in the third stage the amount was reduced to 0·1 g. to enable measurements to be made in the range 5—0%. Measurements on systems containing more than 70% of diphenyl ether presented difficulty owing to the small amounts of water in the equilibrium mixtures. Moreover, systems containing more than 80% of water formed a suspension of fine droplets, and the change from clarity to turbidity was not sufficiently sharp to permit accurate determination of the miscibility points.

In systems of moderately high diphenyl ether content approach to the miscibility point was characterised by the appearance of a marked turbidity which could be cleared by the addition of one drop of the third component. Intense opalescence was invariably observed in the neighbourhood of the plait point, and the measurements in this region were the most accurate of the series. The sharpness of the end-points deteriorated with increasing concentration of water in the systems.

An indication of the accuracy attainable by the use of the present apparatus is furnished by the data for the system containing butanol. The binodal curve for this system is found to cut the water–butanol axis at a point corresponding to 20·25% of water, which is very close to the value (20·27%) recorded by Hill and Malisoff (*J. Amer. Chem. Soc.*, 1926, **48**, 918) for the solubility of water in this alcohol at 25°.

The miscibility data and the refractive indices of the solutions are recorded in Table 1.

The binodal curve can be formulated mathematically by referring the miscibility data to rectangular co-ordinates, one comprising the base of the triangle and the other drawn at right angles at the end of the base. Separate cubic equations can then be developed to represent the two curves on either side of the summit of the binodal curve. The limits of the equation are expressed in terms of x, the concentration of water in moles % on the two co-ordinate diagram.

Values of the co-ordinate y are obtained in terms of multiples of 10% intervals along the x-axis. By plotting the curve in this way, it is only necessary to draw the equilateral triangle upon the base $x = 0$—100% in order to obtain the actual compositions in terms of the three components. The equations representing the binodal curves of the various systems are of the type

$$(1)\quad y = \alpha x + \beta x^2 + \gamma x^3$$

$$(2)\quad y = \alpha_1(100 - x) + \beta_1(100 - x)^2 + \gamma_1(100 - x)^3$$

where equation (1) represents the diphenyl ether-rich side and equation (2) the water-rich side of the binodal curve. The limiting values of x, and the values of the coefficients in the above equations are given in Table 2. The applicability of the equations is shown by the examples in Table 3.

Determination of Tie-lines.—Mixtures corresponding to points inside the heterogeneous region of the phase diagram were prepared by weighing the components into constricted test-tubes which were then hermetically sealed. The tubes were vigorously shaken in the thermostat

TABLE 1. *Miscibility data.*

Ph_2O, %	H_2O, %	MeOH, %	n_D^{25}
49·26	1·24	49·50	—
42·70	1·50	55·80	—
31·27	2·53	66·20	—
26·59	3·40	70·01	—
22·74	4·76	72·50	—
18·71	6·06	75·23	—

Ph_2O, %	H_2O, %	MeOH, %	n_D^{25}
16·55	7·40	76·05	—
13·20	9·60	77·20	—
9·04	13·75	77·21	—
6·55	17·05	76·40	—
4·11	20·24	75·65	—
4·50	21·70	73·80	—

Ph_2O, %	H_2O, %	MeOH, %	n_D^{25}
2·88	25·12	72·00	—
2·37	27·41	70·22	—
1·45	30·59	67·96	—
1·12	34·08	64·80	—
0·88	35·76	63·36	—
0·31	38·92	60·77	—

Ph_2O, %	H_2O, %	EtOH, %	n_D^{25}
71·35	1·65	27·02	1·5030
67·93	1·95	30·12	1·4953
56·60	3·23	40·17	1·4685
56·09	3·22	40·69	1·4682
49·43	3·88	46·69	1·4541
44·97	4·51	50·52	1·4451
43·75	4·94	51·29	1·4420
36·82	6·50	56·68	1·4325
32·60	7·70	59·70	1·4195

Ph_2O, %	H_2O, %	EtOH, %	n_D^{25}
27·30	9·10	63·60	1·4136
22·30	10·80	66·90	1·4041
19·53	11·76	68·71	1·3968
15·83	14·72	69·45	1·3902
15·34	15·41	69·25	1·3888
13·10	17·10	69·80	1·3860
11·98	18·04	69·98	1·3832
10·97	19·57	69·46	1·3820
10·00	20·70	69·30	1·3804

Ph_2O, %	H_2O, %	EtOH, %	n_D^{25}
8·97	22·60	68·43	1·3788
8·82	21·78	69·40	1·3784
6·55	26·30	67·15	1·3746
6·04	27·70	66·26	1·3738
3·56	33·00	63·44	1·3689
2·00	39·20	58·80	1·3652
2·23	40·80	56·97	1·3641
1·18	44·30	54·52	1·3626
0·71	52·40	46·89	1·3571

Ph_2O, %	H_2O, %	Pr^nOH, %	n_D^{25}
94·34	0·45	5·18	1·5653
84·81	1·33	13·86	1·5422
76·89	2·37	20·84	1·5249
66·90	4·17	28·96	1·5018
64·11	4·60	31·29	1·4959
58·40	5·71	35·89	1·4839
56·65	6·18	37·15	1·4803
47·07	7·93	45·00	1·4616
41·46	9·56	48·98	1·4505

Ph_2O, %	H_2O, %	Pr^nOH, %	n_D^{25}
39·48	10·30	50·22	1·4480
36·36	11·22	52·42	1·4411
29·52	13·73	56·82	1·4289
23·95	16·85	59·20	1·4184
22·75	18·38	59·87	1·4160
19·44	20·86	59·74	1·4098
18·65	21·91	59·44	1·4084
16·37	23·92	59·71	1·4035
14·25	26·60	59·15	1·3995

Ph_2O %	H_2O, %	Pr^nOH, %	n_D^{25}
12·35	28·75	58·94	1·3950
11·05	31·83	57·12	1·3922
9·66	34·41	55·92	1·3884
6·39	41·72	51·89	1·3805
5·34	44·20	50·46	1·3781
3·33	52·66	44·01	1·3702
1·85	60·64	37·53	1·3632
0·98	67·20	32·01	1·3578
0·47	74·50	25·03	1·3528

Ph_2O, %	H_2O, %	Pr^iOH, %	n_D^{25}
68·03	3·66	28·31	1·5032
53·46	4·84	41·70	1·4716
49·39	5·36	45·25	1·4625
40·99	6·35	52·66	1·4460
34·31	8·25	57·44	1·4345
28·06	10·97	60·97	1·4223
22·97	13·98	63·05	1·4120

Ph_2O, %	H_2O, %	Pr^iOH, %	n_D^{25}
18·37	17·17	64·46	1·4029
14·89	20·37	64·74	1·3966
12·64	23·38	63·98	1·3922
8·72	28·47	62·81	1·3858
6·11	33·99	59·90	1·3798
5·13	38·37	56·50	1·3769

Ph_2O, %	H_2O, %	Pr^iOH, %	n_D^{25}
3·64	42·46	53·90	1·3742
2·09	49·91	48·00	1·3689
0·67	59·10	40·23	1·3632
0·42	63·86	35·72	1·3601
0·29	66·70	33·01	1·3583
0·25	68·00	31·75	1·3575

Ph_2O, %	H_2O, %	Bu^nOH, %	n_D^{25}
94·30	0·37	5·33	1·5649
84·80	0·67	14·53	1·5430
78·39	1·32	20·39	1·5298
75·11	1·49	23·40	1·5228
67·72	2·21	30·07	1·5084
63·56	2·75	33·69	1·4991
62·60	2·76	34·64	1·4979
52·10	4·11	43·79	1·4775
49·77	4·51	45·72	1·4730
45·41	5·10	49·49	1·4651

Ph_2O, %	H_2O, %	Bu^nOH, %	n_D^{25}
39·03	6·37	54·60	1·4534
36·47	7·36	56·17	1·4510
28·68	8·89	62·43	1·4357
23·90	9·65	66·45	1·4285
20·20	11·21	68·59	1·4223
15·83	12·96	71·21	1·4141
14·50	12·80	72·70	1·4129
12·55	14·31	73·16	1·4096
9·83	15·06	75·11	1·4049
7·31	16·00	76·69	1·4013

Ph_2O, %	H_2O, %	Bu^nOH, %	n_D^{25}
6·35	16·60	77·05	1·3996
6·00	16·90	77·10	1·3990
3·84	17·54	78·62	1·3954
3·79	17·91	78·30	1·3955
2·15	18·70	79·15	1·3928
1·97	18·64	79·39	1·3917
0·98	19·34	79·68	1·3902
0·67	19·68	79·65	1·3900
0·24	20·10	79·66	1·3891

TABLE 1. (*Continued.*)

Ph_2O, %	H_2O, %	$Me{\cdot}CO_2H$, %	n_D^{25}
77·20	1·00	21·80	1·5282
64·76	1·55	33·69	1·5034
53·76	2·47	44·77	1·4812
52·38	2·65	44·97	1·4792
48·95	3·05	48·00	1·4721
42·61	3·65	53·74	1·4590
36·54	4·60	58·86	1·4465
34·30	5·34	60·36	1·4420

Ph_2O, %	H_2O, %	$Me{\cdot}CO_2H$, %	n_D^{25}
25·96	6·96	67·08	1·4240
23·79	7·41	68·80	1·4201
18·75	9·19	72·06	1·4100
16·13	10·02	73·85	1·4046
13·40	10·96	75·64	1·3995
10·50	12·90	76·60	1·3934
9·04	14·10	76·86	1·3904

Ph_2O, %	H_2O, %	$Me{\cdot}CO_2H$, %	n_D^{25}
7·79	15·17	77·04	1·3878
5·59	17·40	77·01	1·3846
4·65	18·93	76·42	1·3828
4·30	20·07	75·63	1·3817
1·55	26·15	72·30	1·3777
0·68	35·47	63·85	1·3752
0·55	31·45	68·00	1·3741

Ph_2O, %	H_2O, %	$Et{\cdot}CO_2H$, %	n_D^{25}
78·61	1·08	20·31	1·5318
68·63	1·84	29·53	1·5120
61·09	2·86	36·05	1·4975
49·93	5·16	44·91	1·4759
44·16	6·88	48·96	1·4650
38·36	8·70	52·94	1·4551
33·45	10·75	55·80	1·4451
28·60	13·11	58·90	1·4362

Ph_2O, %	H_2O, %	$Et{\cdot}CO_2H$, %	n_D^{25}
23·29	15·74	61·66	1·4263
19·07	18·40	63·55	1·4180
14·67	21·28	64·05	1·4086
12·29	23·90	63·90	1·4032
11·35	24·71	63·94	1·4012
8·25	28·62	63·13	1·3947
6·07	32·32	61·61	1·3889
4·15	37·35	58·52	1·3837

Ph_2O, %	H_2O, %	$Et{\cdot}CO_2H$, %	n_D^{25}
2·97	40·21	56·82	1·3810
2·20	44·45	53·35	1·3769
1·57	57·31	51·12	1·3741
1·03	52·35	46·62	1·3700
0·55	57·01	42·44	1·3662
0·28	62·51	37·21	1·3620
0·09	72·86	27·05	1·3528

Ph_2O, %	H_2O, %	$Pr{\cdot}CO_2H$, %	n_D^{25}
74·71	0·81	24·48	1·5286
62·11	1·75	36·14	1·5051
54·78	2·57	42·65	1·4920
46·54	3·91	49·55	1·4759
40·12	5·54	54·34	1·4634
34·80	7·90	57·30	1·4541

Ph_2O, %	H_2O, %	$Pr{\cdot}CO_2H$, %	n_D^{25}
29·66	9·90	59·44	1·4435
23·73	12·99	63·28	1·4330
20·24	16·49	63·27	1·4255
15·43	21·08	63·49	1·4153
10·59	27·25	62·16	1·4042
6·00	36·40	57·60	1·3930

Ph_2O, %	H_2O, %	$Pr{\cdot}CO_2H$, %	n_D^{25}
3·70	43·68	52·62	1·3835
1·87	57·72	40·41	1·3700
1·07	66·63	32·30	1·3626
0·58	73·15	26·27	1·3565
0·31	77·98	21·71	1·3525

TABLE 2.

Third component	x limit	α	α_1	$10^4\beta$	$10^4\beta_1$	$10^6\gamma$	$10^6\gamma_1$
Methanol	50	0·078	0·081	1·78	6·45	−5·10	−15·60
Ethanol	52	0·064	0·090	2·74	0·19	−8·70	−11·51
Propanol	60	0·062	0·101	−3·95	−10·50	−0·32	− 2·86
*iso*Propanol	55	0·050	0·093	0·89	− 6·65	−2·42	− 2·00
Acetic acid	59	0·045	0·089	1·70	8·00	−7·65	−25·00
Propionic acid	52	0·066	0·086	0·81	− 3·45	−0·10	− 0·11
Butyric acid	50	0·084	0·092	−6·70	−11·81	−1·71	5·00

TABLE 3.

Third component : propanol						Third component : propionic acid					
x	y, calc.	y, obs.	x	y, calc.	y, obs.	x	y, calc.	y, obs.	x	y, calc.	y, obs.
10	0·58	0·58	60	2·24	2·19	10	0·62	0·62	60	2·16	2·15
20	1·08	1·08	70	2·02	2·02	20	1·26	1·26	70	1·99	1·98
30	1·50	1·49	80	1·58	1·52	30	1·76	1·76	80	1·49	1·49
40	1·80	1·82	90	0·89	0·88	40	2·10	2·09	90	0·82	0·85
50	2·08	2·10				50	2·18	2·18			

to establish equilibrium in the system, and were then kept in the bath for several hours to allow separation of the mixture into two liquid layers. The tubes were opened, and a small quantity of each layer was withdrawn by means of pre-heated sampling tubes so that the refractive index could be determined as described previously. The composition of the equilibrium mixture, expressed in terms of the concentration of both diphenyl ether and water, was plotted against the refractive index of the solution, and from the resulting curves the points on the isotherm representing the compositions of the conjugate solutions were ascertained. If, as occasionally happened, the straight line connecting these two points did not pass through the point in the binodal region representing the mixture under examination, the experiment was repeated.

The method gave reproducible results for all the systems except that containing methanol, and the liquid layers of this system were analysed by Karl Fischer's method (*Angew. Chem.*, 1935, **48**, 394). A titration cell being used with platinum electrodes connected with a potentiometer and a sensitive galvanometer, the Karl Fischer reagent was standardised by titration of methanol solutions containing known amounts of water, the operation being conducted in an

TABLE 4. *Tie-line data.*

Wt. (%) in H_2O layer			Wt. (%) in Ph_2O layer			Wt. (%) in H_2O layer			Wt. (%) in Ph_2O layer		
Ph_2O	H_2O	MeOH	Ph_2O	H_2O	MeOH	Ph_2O	H_2O	EtOH	Ph_2O	H_2O	EtOH
28·5	3·2	68·3	85·0	0·5	16·5	18·4	12·2	69·4	92·5	0·4	7·1
17·5	6·9	75·6	92·5	—	7·5	8·6	22·1	69·3	95·4	0·2	4·4
8·9	13·1	78·0	95·5	—	4·5	6·5	25·7	67·8	96·4	0·1	3·4
5·0	19·8	75·2	97·6	—	2·4	1·6	34·9	63·5	96·8	0·1	3·1
1·7	29·0	69·3	98·5	—	1·5	1·3	40·0	58·6	97·6	—	2·3
0·3	38·9	60·8	98·9	—	1·1	0·8	55·0	44·2	98·5	—	1·4
—	57·1	42·9	99·3	—	0·7	0·5	67·6	31·9	99·0	—	1·0
—	71·5	28·5	99·8	—	0·2	0·1	80·1	19·8	99·6	—	0·4
Ph_2O	H_2O	Pr^nOH	Ph_2O	H_2O	Pr^nOH	Ph_2O	H_2O	Pr^iOH	Ph_2O	H_2O	Pr^iOH
26·4	15·7	57·9	81·4	2·0	16·6	33·1	8·7	58·2	79·3	2·2	18·5
22·8	18·4	58·8	83·7	1·6	14·6	21·5	14·5	64·0	86·2	1·5	12·3
15·3	25·7	59·1	85·4	1·2	13·4	16·5	18·5	65·0	89·3	1·1	9·6
8·3	37·3	54·4	86·5	1·2	12·3	11·4	25·0	63·6	91·0	0·9	8·1
4·8	46·2	49·0	87·7	1·0	11·3	5·3	36·8	57·9	93·4	0·6	6·0
2·2	57·0	40·8	87·8	1·0	11·2	2·8	47·6	49·6	95·1	0·5	4·3
0·7	68·0	31·3	88·4	0·9	10·7	0·6	60·4	38·9	96·1	0·4	3·4
0·4	76·0	23·6	90·6	0·7	8·7	0·3	76·0	23·7	97·6	0·4	2·0
0·3	81·0	18·7	92·8	0·5	6·7	0·1	86·6	13·3	98·5	0·1	1·4
0·1	90·6	9·3	98·2	0·2	1·6						
Ph_2O	H_2O	Bu^nOH	Ph_2O	H_2O	Bu^nOH	Ph_2O	H_2O	$Me{\cdot}CO_2H$	Ph_2O	H_2O	$Me{\cdot}CO_2H$
—	97·1	2·9	13·8	13·4	72·8	9·0	14·0	77·0	80·0	0·7	19·2
—	97·1	2·9	22·5	10·0	67·5	3·9	21·2	74·8	87·2	0·6	12·2
—	97·1	2·9	33·5	7·4	59·1	2·6	26·0	71·4	89·7	0·5	9·8
—	97·1	2·9	42·5	5·5	52·0	0·9	33·7	65·4	93·1	0·4	6·5
—	97·1	2·9	55·5	4·1	40·4	0·5	40·0	59·5	94·4	0·3	5·3
—	97·1	2·9	70·9	2·1	27·0	0·3	46·4	53·2	96·6	0·2	3·2
—	97·1	2·9	86·7	0·7	12·6	0·1	53·0	46·9	97·1	0·1	2·7
						0·1	60·0	39·9	98·0	0·1	1·9
						—	75·5	24·5	99·4	—	0·6
Ph_2O	H_2O	$Et{\cdot}CO_2H$	Ph_2O	H_2O	$Et{\cdot}CO_2H$	Ph_2O	H_2O	$Pr{\cdot}CO_2H$	Ph_2O	H_2O	$Pr{\cdot}CO_2H$
16·5	19·9	65·6	52·0	4·8	43·2	0·4	78·6	21·0	4·4	40·2	55·4
10·3	25·5	64·2	61·0	3·0	36·0	0·3	83·4	16·3	12·4	25·1	62·5
6·5	31·9	61·6	68·6	2·0	29·4	0·3	83·6	16·1	13·8	23·8	62·4
4·8	35·3	59·9	71·6	1·6	27·8	0·2	84·4	15·3	22·1	14·8	63·1
2·4	42·7	54·9	77·0	1·2	21·8	0·2	86·1	13·7	39·5	5·7	54·8
1·1	51·0	48·0	81·6	1·0	18·4	0·1	87·7	12·2	52·1	3·0	44·9
0·5	56·3	43·1	84·9	0·6	14·5	0·1	88·1	11·8	58·8	1·9	29·2
0·4	63·1	36·5	88·1	0·5	11·4	0·1	89·4	10·5	69·4	1·4	29·2
0·2	70·0	29·7	91·0	0·4	9·6	—	90·6	9·3	72·6	1·0	26·4
						—	93·0	7·0	85·9	0·4	13·7
						—	94·8	5·2	92·6	0·2	7·2

atmosphere of dry nitrogen. The reagent was used in a similar manner to determine the water content of the conjugate solutions. The method was also applied to determination of the water content of the water-rich layers in the system containing butanol. The tie-line data for the systems are tabulated in Table 4.

DISCUSSION

The binodal curves and tie-lines for systems of diphenyl ether, water, and various third components are shown in Figs. 2—9, where the compositions are expressed in moles %. For the range of alcohols studied the slope of the tie-lines becomes less as the homologous series is ascended, and this feature, revealing as it does the increasing preference of the alcohol for the diphenyl ether layer, is most marked for butanol, which is only partially miscible with water. The same phenomenon is evident in the acid systems, and acetic acid strongly favours the aqueous phase while butyric acid favours the diphenyl ether phase to roughly the same extent. Although no simple relation is apparent between the position of the plait point in the phase diagram and the chain length of the alcohol, yet it is found that the summit concentration is given by $100—16{\cdot}7n$, where n is the number of carbon atoms in the alcohol molecule. A similar influence of homology is found in hydrocarbon–water–alcohol systems, where there is a decrement of about 21 moles % in the summit

concentration for each additional carbon atom in the molecule of the third component. No such relation applies, however, when the third component is a fatty acid.

FIG. 2.

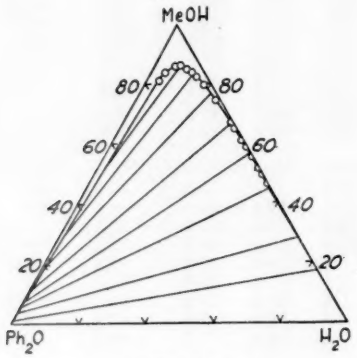


FIG. 3.

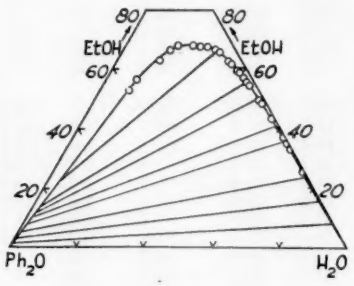


FIG. 4.

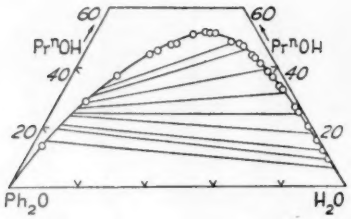


FIG. 5.

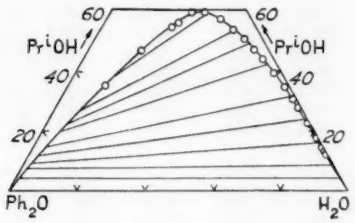


FIG. 6.

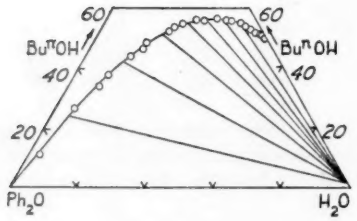


FIG. 7.

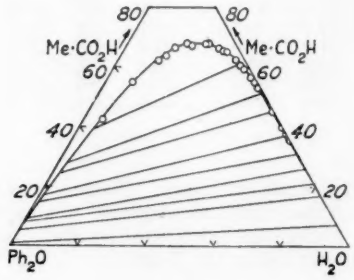


FIG. 8.

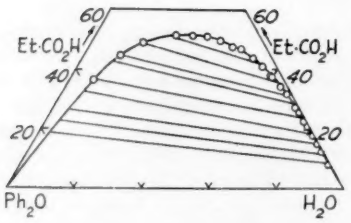
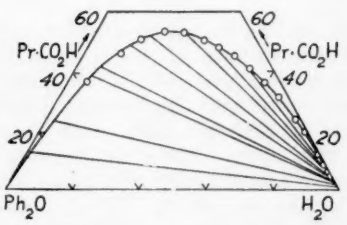


FIG. 9.



Solutropism involves the reversal of slope of the tie-lines, and the phenomenon has been shown to occur in some 30 systems when composition is in weight %, and in 35 systems when the composition is expressed in moles % (Smith, Stibolt, and Day, *Ind. Eng. Chem.*,

1951, **43**, 190). None of the systems examined in the present work is found to be solutropic on the former basis, but, as shown in Fig. 4, the system containing propanol exhibits the phenomenon when the composition is expressed in moles %.

According to Tarasenkov and Paulsen (*J. Phys. Chem., U.S.S.R.*, 1940, **14**, 1940), accurately determined tie-lines meet at a point focus when produced outside the binodal curve. In this connexion, Brancker, Hunter, and Nash (*Ind. Eng. Chem. Anal.*, 1940, **12**, 35) state that " insufficient information is available to determine whether the point focus is a general case and whether any deviations therefrom may be due, as is not completely improbable, to inaccurate tie-line data, to the presence of an unsuspected fourth component or to compound formation." The validity of the hypothesis can be tested on the systems under study inasmuch as the internal evidence shows that the tie-line data are of high precision. The test, which is made by plotting the data in terms of weight %, reveals that the systems containing methanol, ethanol, acetic acid, and propionic acid have tie-lines meeting at a point focus, whereas the tie-lines for each of the other systems meet to produce a caustic curve. In view of the close similarity between the chemical structures of the homologous components in these two types of system, it is highly improbable that compound formation is responsible for the different character of the tie-lines. We conclude accordingly that the point-focus hypothesis has no general validity and that tie-line correlation is not feasible on this basis.

The data obtained in the present work may also be used to assess the accuracy of the various methods of tie-line correlation. The reliability of the experimental measurements is shown by the fact that a smooth conjugation curve is obtained when the data are plotted in accordance with Coolidge's method (I.C.T., 1926, III, 398). The composition of each system at the plait point (corresponding to the intersection of conjugation and binodal curves) is given in section (*a*) of Table 5.

TABLE 5. *Composition in moles % at plait point.*

Third component of system	(*a*)			(*b*)		
	Ph_2O	H_2O	Third component	Ph_2O	H_2O	Third component
Methanol	22·20	4·60	73·20	22·40	2·80	74·80
Ethanol	58·15	6·47	35·38	55·80	6·90	37·30
n-Propanol	29·70	24·30	46·00	39·10	19·50	41·40
*iso*Propanol	27·20	19·90	52·90	25·00	20·40	54·60
Acetic acid	39·10	7·80	53·10	25·30	12·00	62·70
Propionic acid	13·10	38·10	48·80	13·40	36·80	49·20
n-Butyric acid	0·05	92·10	7·85	0·05	92·70	7·25

According to Bancroft (*Phys. Review*, 1896, **3**, 21) and Lincoln (*J. Phys. Chem.*, 1900, **4**, 160), the equilibrium at constant temperature may be expected to conform to a mass-law equation of the type $(w_2/w_3)^m/(w_1/w_3) = K$, where w_1 and w_2 are the respective weights of immiscible liquids in a fixed weight w_3 of consolute liquid, and m and K are constants. The plot of log (w_2/w_3) against log (w_1/w_3) for each of the systems under study gives a sigmoidal curve, and the departures from the linear relation are much larger than can be accounted for by experimental error. The equilibrium in several systems was found by Hand (*ibid.*, 1930, **34**, 1961) to conform to the equation $X_{31}/X_{11} = k(X_{32}/X_{22})^m$, where k and m are constants, X is weight fraction, and the subscripts refer to the three components, respectively. For the present systems, however, the logarithmic plot of X_{31}/X_{11} against X_{32}/X_{22} generally yields three straight lines of different slope as is found for other systems (Campbell, *Ind. Eng. Chem.*, 1944, **36**, 1158; Frere, *ibid.*, 1949, **41**, 2365). Although the equation is not applicable over the whole composition range, it may be used to determine the composition of the system at the plait point. The compositions evaluated in this way are recorded in section (*b*) of Table 5, and are more accurate than those listed in section (*a*) inasmuch as the plot based on Hand's relation is linear in the region of the plait point and extrapolation can be made with precision.

Bachman's method (*Ind. Eng. Chem. Anal.*, 1940, **12**, 38) has been extended by Othmer and Tobias (*Ind. Eng. Chem.*, 1942, **34**, 693), who find that a linear correlation is obtained by plotting log $[(1 - a_1)/a_1]$ against log $[(1 - b_2)/b_2]$, where a_1 is the fraction of the non-

consolute liquid a in the layer mainly composed of a, and b_2 is the fraction of the other layer which is the non-consolute liquid b. Although for the majority of the systems examined in the present work the plot yields three intersecting lines, the superiority of the method is evident, and is further revealed by the fact that one straight line is obtained for the systems containing acetic acid and propionic acid, severally.

An interesting attempt to devise a variable ordinate scale based upon the tie-line relation of a " standard " system (water, toluene, acetic acid) has been made by Brancker, Hunter, and Nash (*loc. cit.*), who state that the plot of the relation between the weight percentages of the non-consolute liquids present in conjugate phases yields straight lines for a large number of systems, and that anomalies may be attributed to the presence of a fourth component or to inaccurate tie-line determinations. In this connexion, Dr. Brancker (personal communication) has pointed out that anomalies would also arise if there are factors retarding the attainment of equilibrium. When plotted on the above basis, the present data are found to conform to a linear relation over the entire composition range for the system containing ethanol, but the linear relation holds only over a limited range in the case of the other systems. Since there is no experimental evidence of compound formation in these systems, and independent tests reveal that the tie-line data are accurate and refer to completely equilibrated phases, it appears that the use of a variable ordinate scale in this way is not of general applicability.

We are indebted to Dr. A. V. Brancker for helpful discussion of the applicability of correlation methods.

TATEM LABORATORIES,
UNIVERSITY COLLEGE, CARDIFF. [*Received, September 4th*, 1953.]

The Thermal Decomposition of tert.*-Butylamine.*

By H. O. PRITCHARD, R. G. SOWDEN, and A. F. TROTMAN-DICKENSON.

[Reprint Order No. 4651.]

The thermal decomposition of *tert.*-butylamine has been studied in a static system in the temperature range 498—541° and over the pressure range 5—18 cm. The reaction was followed by pressure measurements and by analysis of the products. The pressure increase is due to the alternative simultaneous homogeneous first-order molecular scissions :

$$CMe_3{\cdot}NH_2 \longrightarrow CMe_2{:}CH_2 + NH_3 \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$CMe_3{\cdot}NH_2 \longrightarrow C_3NH_7 + CH_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

together with a subsequent slow reaction of the products, for which a correction can be readily applied. The ratio of ammonia to methane was 1 : 2·5 ± 0·1 over the temperature range studied, indicating that the activation energies of reactions (1) and (2) do not differ by more than 1 kcal./mole. A least-squares Arrhenius plot gave an overall rate constant

$$k = 10^{14\cdot79} \exp(-67{,}100/\boldsymbol{R}T) \text{ sec.}^{-1}.$$

A LARGE number of unimolecular decompositions are known in which one molecule splits directly into two normal molecules. These reactions may be called " molecular-split " reactions, to distinguish them from reactions in which free radicals are formed. The simplest reactions of this class are those which occur through a transition state containing a ring of four atoms and they are often called four-centre reactions. The activation energies of many of these reactions have been measured. In Table 1 are given the activation energies of some of the simplest of them (including the results of this research). However, no satisfactory interpretation of the variations in their activation energies has yet been given. In an attempt to throw light on the general theoretical problem by provision of further results the decompositions of ethanethiol and *iso*butanethiol (2-methyl-

propane-2-thiol) were examined. Our experimental results with the former are exactly similar to those of Trenner and H. A. Taylor (*J. Chem. Phys.*, **1933**, **1**, 77), though we regard their mechanism involving the initial formation of polysulphides as rather improbable since the sulphur–sulphur bond is not strong. Very similar results were found by us with *iso*butanethiol so that it was not suitable for the present purpose either. This was disappointing, as a consideration of the bond strengths might lead one to suppose that the behaviour of the alkanethiols would be similar to that of the alkyl chlorides and bromides. The decomposition of *tert.*-butylamine was expected to occur smoothly because

TABLE 1. *Activation energies (in kcal./mole) of reaction of the type* $CH_3{\cdot}CR_2X \longrightarrow CH_2{:}CR_2 + HX$.

$CH_3{\cdot}CR_2X$	HX: HCl	HBr	H_2O	NH_3	CH_4
Et X	60·8 [a]	53·9 [d]	—	—	—
Pr^{i}X	50·5 [b]	47·8 [d]	—	—	—
Bu^{t}X	41·4 [c]	42·2 [d]	65·5 [e]	67·1 [f]	59·3 [g]
Bu$^t{\cdot}NH_2$	—	—	—	67·1 [f]	67·1 [f]

[a] Barton and Howlett, *J.*, 1949, 148. [b] Barton and Head, *Trans. Faraday Soc.*, 1950, **46**, 114. Barton and Onyon, *ibid.*, 1949, **45**, 725. [d] Blades and Murphy, *J. Amer. Chem. Soc.*, 1952, **74**, 6220; Green, Harden, Maccoll, and Thomas, *J. Chem. Phys.*, 1953, **21**, 178. [e] Schultz and Kistiakowsky, *J. Amer. Chem. Soc.*, 1934, **56**, 395. [f] This work. [g] Peard, Stubbs, and Hinshelwood, *Proc. Roy. Soc.*, 1952, *A*, **214**, 330.

of its similarity to *tert.*-butanol. It was found that *tert.*-butylamine decomposed by way of the two molecular-split mechanisms (1) and (2) (above), having rate constants given respectively by the expressions $k_1 = 1{\cdot}7 \times 10^{14} \exp(-67{,}000/\boldsymbol{R}T)$ sec.$^{-1}$ and $k_2 = 4{\cdot}4 \times 10^{14} \exp(-67{,}000/\boldsymbol{R}T)$ sec.$^{-1}$. This is of interest because examples of a molecule reacting by two distinct molecular-split mechanisms are rare, though of course, numerous reactions are known which proceed by different ionic or free-radical mechanisms.

However, this work has complicated rather than clarified the general problem of the factors affecting the activation energy of molecular-split reactions.

EXPERIMENTAL AND RESULTS

Materials.—*tert.*-Butylamine (B.D.H.), distilled through a 30-plate column (reflux ratio 8 : 1), had b. p. 64·2°/757 mm. The toluene was a highly purified sample. Before use the reagents were carefully degassed by bulb-to-bulb distillation *in vacuo*.

Apparatus and Procedure.—The reaction vessel was a 2-l. Pyrex bulb supported in a thermostatically controlled furnace, as used in our previous work (*Proc. Roy. Soc.*, 1953, *A*, **217**, 563). The reaction was followed by means of a mercury manometer connected to the reaction vessel.

Results.—A typical plot of the logarithm of (initial pressure − pressure increase) against time is shown in Fig. 1. An initial fast reaction is observed, followed by a first-order reaction represented by the linear portion of the curve, which appears to accelerate after about two half-lives as is shown by the downward curvature of the plot. This curvature is believed to be caused by a secondary reaction of the products of the main reaction. The addition of toluene had no effect on the slope of the linear portion of the graph but eliminated the initial fast reaction. This was therefore supposed to be an alternative method of decomposition which proceeded by a free-radical chain mechanism; it was suppressed by the toluene when it was present or, when no toluene had been added, by the chain inhibitors (such as butene) produced in the decomposition. This hypothesis was tested by admitting more *tert.*-butylamine into the reaction vessel during a run. As predicted, the fast reaction did not recur.

The rate constant (k_3) for the secondary reaction (3) (the nature of which is discussed in a later section of this paper), was found by following the pressure increase after the main reaction had proceeded virtually to completion. It was assumed that this reaction also was a molecular split in which one of the product molecules split in two. Any other reasonable assumption would be equally good for the present purpose. Let k be the rate constant of the principal reaction; then $k \gg k_3$, and it can be shown that a correction for the second reaction may be made by subtracting a quantity $p_0(1 - e^{-k_3 t})$ from the observed pressure at a time t, where p_0 is the initial pressure of the reactant. At 527°, k_3 was less than $0{\cdot}05k$ and this simple correction was shown to be justified. k_3 was determined only at 527° because the measurement was

lengthy and little error could be introduced by assuming that reaction (3) has the same temperature coefficient as the main reaction. An Arrhenius plot of the results is given in Fig. 2 for runs with initial pressures of reactant between 5 and 18 cm. The straight line corresponding to the equation $k = 6{\cdot}1 \times 10^{14} \exp(-67{,}100/RT)$ sec.$^{-1}$ was obtained by the method

FIG. 1. *Typical plot of logarithm of (initial pressure—pressure increase) against time.*

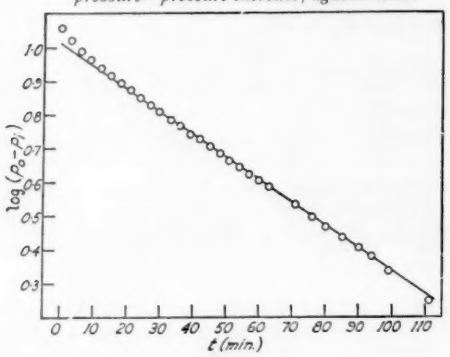
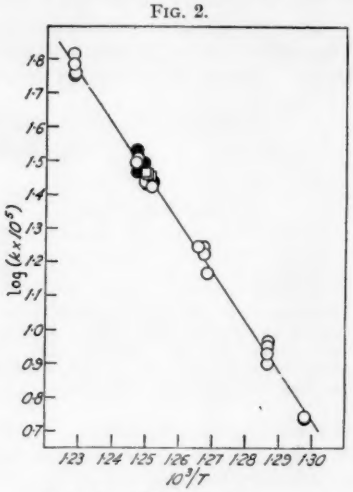


FIG. 2.



Arrhenius plot of results :
○ *Runs in unpacked vessel.*
● *Runs in packed vessel.*
□ *Runs with toluene.*

of least squares, based only on the values obtained in an unpacked vessel in the absence of toluene. It can be seen that the values obtained in the presence of toluene and in a packed vessel of eight times the surface area of the unpacked vessel show no deviations outside the experimental error.

Analysis.—At the end of a run the stopcock S_1 was opened to admit the products into the analysis system shown in Fig. 3. At first with stopcocks S_2 and S_4 closed the gases were pumped

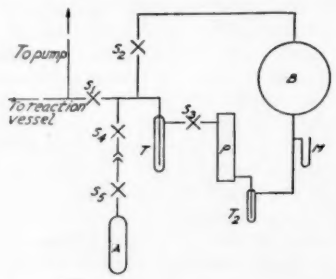


FIG. 3. *Diagram of analysis apparatus.*

by the two-stage mercury-diffusion pump P, through the pumped-down nitrogen-cooled trap T at $-217°$, into the 2-l. bulb B, to which a manometer M was attached. All the products except the hydrogen, which was subsequently identified by absorption in the heated copper oxide tube T_2, were condensed out and the pressure of the hydrogen was measured.

T was then warmed to the temperature of liquid oxygen, and the pressure of methane measured, after which the non-condensable gases were pumped away. The pressures in the system when T was at a temperature of $-78°$ and at room temperature were then measured. These measurements gave the pressure of products whose composition will be considered later, and the total amount of gas withdrawn from the reaction vessel. The whole mixture was then distilled into the bulb A, which contained an excess of previously degassed dilute sulphuric

acid; *A* was removed from the system, allowed to warm, shaken to ensure satisfactory gas absorption, reattached to the vacuum-system, and cooled with solid carbon dioxide. Then the pressure of non-basic volatile gases was measured. As the amines present in the products were not volatile at −78°, the difference in the pressures read with the products at this temperature, before and after absorption, gave the pressure of ammonia in the products. The volatile products were then shaken with concentrated sulphuric acid to absorb unsaturated compounds. It was found that an amount of gas equal to the amount of hydrogen formed in the reaction was not absorbed by the acid. By its vapour pressure this gas was identified as propane. It was established empirically for seven runs that the identity

$$\text{Pressure of gas volatile at } -78° = 2 \times \text{pressure of } NH_3 + 2 \times \text{pressure of } H_2$$

held. This was used for calculating the ratios of methane to ammonia produced. It may be interpreted by supposing that an amount of *iso*butene is formed equal to the amount of ammonia as is required by reaction (1), and that the hydrogen is produced by the secondary reaction (3) by which an equivalent amount of propane and of some other gas that is absorbed by sulphuric acid are also produced. We have not been able to continue a plausible reaction scheme to account for these products and they may be produced by a rather complex mechanism. However, the gases only represent some 4% of the total products. The hypothesis receives some confirmation from the reasonable agreement between the amount of hydrogen produced and the amount calculated by assuming that it is produced by reaction (3) (cf. cols. 5 and 6 of Table 2).

The complete analytical results, given in Table 2, show that the conversion calculated from the pressure change in the reaction vessel is always some 10—15% higher than that calculated from the analytical results except for the two runs to which toluene was added. We believe that the discrepancy is caused by the formation by the initial rapid reaction of products which

TABLE 2.

Run	Temp.	Total press.*	H_2*	$\frac{H_2}{Total}$, %	Calc. % corr.	CH_4*	NH_3*	$\frac{CH_4}{NH_3}$	Conversion, %, by: pressure change	Conversion, %, by: analysis
16	498°	5·033	0·111	2·2	2·6	1·107	0·436	2·54	37·8	32·8
20	498	4·738	0·117	2·5	2·6	0·971	0·406	2·39	34·9	31·5
21	498	—	0·075	—	—	1·031	0·418	2·47	—	—
26A	516	4·868	0·091	1·9	1·2	0·845	0·330	2·56	29·6	26·0
29	516	4·715	0·110	2·3	1·8	0·965	0·378	2·55	35·0	—
30	516	5·120	0·116	2·3	1·7	0·984	0·374	2·63	34·9	28·8
33	541	—	0·108	—	—	0·911	0·348	2·62	—	—
35	541	—	0·084	—	—	0·781	0·336	2·32	—	—
37	541	—	0·103	—	—	0·948	0·385	2·46	—	—
† 48	§ 527	3·938	0·104	2·6	1·3	0·700	0·266	2·64	28·0	27·1
† 48A	§ 527	3·824	0·091	2·4	1·6	0·671	0·289	2·32	28·8	27·8
† 48B	527	5·148	0·116	2·3	1·6	1·116	0·433	2·58	34·9	32·3
† 48C	527	5·061	0·127	2·5	1·5	1·047	0·366	2·86	34·1	30·5

* These pressures are in cm. in the analysis system and have no absolute significance.
† Run in packed vessel. § Run with added toluene.

polymerise on leaving the reaction vessel. This view is supported by the observation of a deposit in the connecting tubes and the trap *T*, and by the fact that if a correction is made for the products formed in the free-radical reaction the two methods of calculating the conversions agree very well. Accordingly, it may be concluded that the main reactions are those suggested here.

The exact nature of the substance C_3NH_7 is not known. It could be $CMe_2{:}NH$, which might well exist in the gas phase, or $NH_2{\cdot}CMe{:}CH_2$. It does not seem likely that a suitable analytical method could be devised to detect these products in the quantities found here, but some light might be thrown on this problem by studying the decomposition of $(CH_3)_3C{\cdot}ND_2$ as the methane formed would be CH_4 or CH_3D, depending upon whether the carbon atom drew its hydrogen from the amino- or from a methyl group. The compound C_3NH_7 is certainly a derivative of either the keto- or the enol form of acetone, for acetone diphenylhydrazone was obtained from the solution of the amine in dilute sulphuric acid.

THE UNIVERSITY, MANCHESTER, 13.

[*Received, September 14th*, 1953.]

Conductivity and Solubility Studies of Some Glycollates and Lactates.

By W. P. Evans and C. B. Monk.

[Reprint Order No. 4603.]

Conductivity measurements for a number of glycollates and lactates in aqueous solution at 25°, and the dissociation constants of the ion-pairs MR^+, are reported. The cupric salts have been studied by a solubility method, and the dissociation constants of CuR^+ and CuR_2 calculated. The results are discussed in terms of ionisation potentials and cation radii.

As a continuation to previous systematic studies of salts of monocarboxylic acids (Lloyd, Wycherley, and Monk, *J.*, 1951, 1786; Colman-Porter and Monk, *J.*, 1952, 4363), a number of glycollates and lactates have been examined in order to gain further information on the factors which influence ionisation in these systems. These two anions were chosen since the available evidence (*loc. cit.*) indicates that they are ligands with a moderate capacity for complex formation; they are not so powerful for instance as the aminoacetate (*loc. cit.*) or ethylenediaminetetra-acetate (Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798), but are considerably stronger than others such as the propionate and acetate (Colman-Porter and Monk, *loc. cit.*). A comparison of the dissociation constants of the ion pairs or complexes formed does not, however, point to any one physical factor whereby one can correlate the values obtained between a particular anion and a series of cations. The alkaline earths are an example of this. With the anions from glycine and alanine (Colman-Porter and Monk, *loc. cit.*) and some other strong ligands such as those listed by Williams (*J.*, 1952, 3770), the pK values decrease in the order Mg, Ca, Sr, Ba. The glycollate and lactate order is Ca, Mg, Sr, Ba, and this order also occurs with such weak ligands as acetates and propionates. This distinction is not clear-cut, however, for we also find magnesium out of position with some of the strong ligands (Williams, *loc. cit.*), and this feature has been discussed by Williams in a survey covering both organic and inorganic salts of the alkaline earths. It is evident that various factors such as ion size, ionisation potentials, cation hydration, anion ring size, and heat and energy changes all need consideration in attempting to explain the pK orders.

A survey including a large number of cations might be helpful in clarifying the position, and this has been the main object of the present work. Both of the anions considered, given cations of relatively strong bases, form salts which can be studied by conductivity methods. The acids, having pK values of about 4, do not give rise to serious hydrolytic effects, and the slight amount of hydrolysis which would occur is easily suppressed by adding a trace of free acid. This precaution was taken, the pH being kept near 6, and since these solutions were thereby buffered, small corrections for the mobile hydrogen ion had to be made.

Experimental

The conductivity apparatus and general technique have already been described (Davies, *J.*, 1937, 432; Davies and Monk, *J.*, 1949, 413). The cell constants were determined by using a conductivity equation for dilute solutions of potassium chloride (Jenkins and Monk, *J. Amer. Chem. Soc.*, 1950, **72**, 2695). Conductivity water was prepared by passing distilled water through a mixed bed of ion-exchange resins (Dowex C211 and A244). All measurements were made at 25° ± 0·01°, and a purified nitrogen stream was maintained over the cell solutions throughout each run.

Zinc lactate was precipitated by mixing solutions of " AnalaR " lactic acid and zinc sulphate, and adding ammonium hydroxide. It was recrystallised from aqueous ethanol till free from sulphate, and finally from conductivity water. Cadmium lactate was similarly prepared, but the first precipitation was slow, complete crystallisation taking about 2 weeks. Manganese lactate was made by warming an excess of the carbonate with lactic acid for some hours beyond the time when carbon dioxide evolution had finished, filtering, cooling, and recrystallising as in the case of the zinc salt. Sodium lactate solutions were prepared by neutralisation with

carbonate-free sodium hydroxide of lactic acid formed by the passage of zinc lactate solutions through a bed of " Amberlite " I.R.100 resin in the hydrogen form. Nickel lactate was too soluble to be prepared by precipitation methods, so lactic acid formed as above was passed through a bed of " Amberlite " A.R.400 resin in the hydroxyl form. Nickel chloride was then passed on to this and the pH of the resulting nickel lactate solution adjusted with a trace of lactic acid.

Calcium glycollate was formed by refluxing an excess of " AnalaR " calcium carbonate and chloroacetic acid for some hours beyond the point where carbon dioxide evolution had ceased to ensure that all the acid had been converted into the glycollate form. The hot solution was filtered and cooled, and the product recrystallised until chloride-free, first from aqueous ethanol and then from conductivity water. This salt was used to make sodium glycollate by the ion-exchange method just described. Nickel glycollate solutions were also made by the ion-exchange method used for the lactate. Zinc and manganese glycollates were made by the method used for the calcium salt, zinc oxide and manganese carbonate being used. This method was also used for cadmium glycollate, but the solution required filtering through asbestos to remove colloidal matter. These last three salts were recrystallised from aqueous ethanol, and finally from conductivity water.

Considerable care was taken to ensure that the concentrations of the stock solutions were known accurately, and at least two independent solutions were used. Zinc concentrations were found by the gravimetric pyrophosphate method ($\pm$0·02%), nickel was estimated by dimethylglyoxime ($\pm$0·05%), and the cadmium and manganese solutions were made up by weight after dehydrating the crystals at 80° in a vacuum oven. Attempts were made to dry the manganese salt at 100°, but it turned slightly brown and was slightly heavier than when dried to constant weight at 80°. A check by the pyrophosphate method indicated that drying at 80° was complete to within $\pm$0·1%. Cadmium salts dried at 100° had the same weight as if dried at 80°. Sodium hydroxide solutions were standardised under carbon dioxide-free conditions against potassium hydrogen phthalate ($\pm$0·1%). In the case of the cobalt and lead salts where a mixture method was used, gravimetric determinations of chloride were made ($\pm$0·02% and $\pm$0·05% respectively).

The solubility method used for the copper salts was that described by Lloyd, Wycherley, and Monk (*loc. cit.*).

Results.—The limiting anion mobilities were required when interpreting the conductivity measurements, and these were obtained from the sodium salts. Martin and Tartar (*J. Amer. Chem. Soc.*, 1937, **59**, 2672) measured the conductivities of sodium and potassium lactates and derived 38·75 for the lactate ion. Application of Onsager's method of extrapolation (*Physikal. Z.*, 1927, **28**, 277) puts this slightly higher (38·9) and shows at the same time that these salts are completely ionised. Our sodium lactate figures give 35·5, and this considerably lower value can perhaps be attributed to the difference between the methods of preparing the acid, for Martin and Tartar distilled their samples three times under vacuum, whereas we prepared solutions by the hydrogen ion-exchange method described above. The distillation of lactic acid causes condensation polymerisation (see Montgomery, *J. Amer. Chem. Soc.*, 1952, **74**, 1466). Even in dilute solution lactyl-lactic acid is present, and according to Watson (*Ind. Eng. Chem.*, 1940, **32**, 399) it takes several weeks for this to change into lactic acid at room temperature. These factors may account for the differences between Martin and Tartar's figures and ours. By precipitating lactates and converting them into the acid by the resin method, the solutions should be quite free from condensation products. Our figures for sodium glycollate (Table 2), which was also prepared by the resin method, give 40·8 for the limiting mobility of the glycollate ion. No comparable figures have been found, but 390 is quoted for the acid (I.C.T., Vol. VI, p. 262), which, since the value for hydrogen is 349·8 (Harned and Owen, " The Physical Chemistry of Electrolytic Solutions," Reinhold, 1950, p. 172), gives the similar figure of 40·2.

The conductivities of the various salts MR_2, where M^{++} is a bivalent cation and R^- represents glycollate or lactate, can be quantitatively discussed by the method of Davies and Righellato (*Trans. Faraday Soc.*, 1930, **26**, 592). The equilibrium concerned is $MR^+ \rightleftharpoons M^{++} + R^-$, and if α represents the fraction of cations which form MR^+ ion-pairs, then since

$$\mu m = \Sigma \mu_i m_i$$

(μ = molecular conductivity of a solution of molarity m, and subscript " i " signifies ions) we have

$$\Lambda = \lambda_M(1 - \alpha) + \lambda_R(2 - \alpha)/2 + \lambda_{MR}\alpha/2$$

(Λ = equivalent conductivity, λ = ion-equivalent conductivity). Rearranging, we have

$$\Lambda = \Lambda_1(1 - \alpha) + \Lambda_2\alpha/2$$

where $\Lambda_1 = \lambda_M + \lambda_R$, and $\Lambda_2 = \lambda_{MR} + \lambda_R$. Both Λ_1 and Λ_2 can be calculated from the corresponding Onsager equations,

$$\Lambda_1 = \Lambda^0_1 - b_1 I^{\frac{1}{2}} \text{ and } \Lambda_2 = \Lambda^0_2 - b_2 I^{\frac{1}{2}}$$

and thus α obtained. In these expressions, b_1 and b_2 are the theoretical Onsager values, and the ionic strength is given by $I = c(1{\cdot}5 - \alpha)$, where c = equivalents per litre. As a charged ion-pair is involved, an assumption has to be made, and we have taken $\lambda^0_{MR} = 0{\cdot}5\lambda^0_M$. Some evidence that such a ratio is of the right order can be obtained by comparing the mobilities of the anions of some bivalent acids A^{2-} with those of the corresponding HA^- ions. Thus Davies *J.*.., 1939, 1850) calculated for three organic acids that the ratio is 0·6, 0·59, and 0·52. Sherrill and Noyes's data for the conductivity of the HSO_4^- ion (*J. Amer. Chem. Soc.*, **1926**, **48**, 1861) extrapolate to 51·5, whence, taking the value for SO_4^{2-} as 80·0 (Jenkins and Monk, *loc. cit.*), we

TABLE 1. *Limiting mobilities and Onsager slopes.*

	Glycollates				Lactates			
	Zn	Ni	Cd	Mn	Zn	Ni	Cd	Mn
Λ^0_1	93·6 [b]	94·5 [a]	93·5 [b]	93·85 [a]	88·3 [b]	89·2 [a]	88·2 [b]	88·55 [a]
Λ^0_2	67·2	67·6	67·1	67·3	61·9	62·3	61·8	62·0
b_1	130·6	131·1	130·6	130·7	129·1	129·5	129·2	129·2
b_2	75·5	75·6	75·5	75·5	74·3	74·4	74·3	74·4

[a] Ni = 53·7, Mn = 53·05 (Jones, Monk, and Davies, *loc. cit.*). [b] Zn = 52·8, Cd = 52·7 by adjusting Λ^0 until the K values showed no significant drifts with concentration; cf. Zn = 53·0 (Owen and Gurry, *J. Amer. Chem. Soc.*, 1938, **60**, 3074).

TABLE 2. *Conductivities of glycollates.*

Run	10^4c	Λ	10^4I	$10^3\alpha$	10^3K	Run	10^4c	Λ	10^4I	$10^3\alpha$	10^3K
		Nickel						Zinc			
2	15·326	79·02	20·39	16·94	5·57	1	6·196	82·50	9·52	12·37	3·98
1	20·191	75·85	25·88	21·41	5·20	2	6·944	82·47	9·55	12·42	3·97
2	22·145	75·35	28·39	21·84	5·50	2	9·856	80·07	13·26	15·50	4·18
1	24·944	74·09	31·52	23·53	5·50	2	13·858	77·20	18·11	19·34	4·27
1	28·957	72·76	36·04	25·19	5·65	1	13·946	77·21	18·23	19·31	4·31
2	29·028	72·32	36·19	25·33	5·64	2	20·250	73·53	25·45	24·37	4·36
2	34·165	70·50	41·59	28·44	5·45	1	24·101	71·63	29·64	27·04	4·35
2	42·114	67·75	49·52	32·40	5·30	1	31·953	68·19	37·71	32·03	4·27
		Cadmium						Manganese			
2	19·750	81·25	27·68	9·74	13·6	2	7·067	88·24	10·43	2·45	23·9
1	21·804	80·50	30·40	10·58	13·5	1	10·409	86·86	15·28	3·35	24·6
2	24·810	79·50	34·34	11·65	13·5	1	12·769	86·06	18·66	3·84	25·7
1	25·848	79·25	35·70	11·85	13·7	2	14·042	85·67	20·48	4·07	26·2
2	29·388	78·20	40·25	12·98	13·7	1	17·285	84·70	25·15	4·70	27·1
1	31·743	77·50	43·23	13·80	13·6	2	19·342	84·10	28·03	5·14	27·1
1	40·139	75·38	53·70	16·11	13·6	1	20·026	83·88	28·96	5·34	26·9
2	40·566	75·22	54·25	16·32	13·5	2	30·725	81·38	43·83	7·27	27·7
1	55·039	72·37	71·78	19·30	14·0						
					Sodium						
2	8·409	88·57	—	—	—	3	15·44	87·71	—	—	—
1	8·672	88·51	—	—	—	1	19·03	87·32	—	—	—
3	10·483	88·28	—	—	—	3	21·955	87·17	—	—	—
1	13·41	87·89	—	—	—	2	25·53	86·85	—	—	—
2	13·45	87·91	—	—	—	3	49·355	85·43	—	—	—

obtain a ratio of 0·64. The limiting mobilities of the HCO_3^- and CO_3^{2-} ions are 44·4 (Shedlovsky and MacInnes, *J. Amer. Chem. Soc.*, **1935**, **57**, 1705) and 69·6 (Monk, *J.*, 1949, 429), respectively, giving a ratio of 0·64. The available evidence therefore points to an upper limit of $\lambda^0_{MR} = 0{\cdot}65\lambda^0_M$, and calculation with, *e.g.*, our data for manganese and nickel lactates over a concentration range using this ratio lowers the dissociation constants by about 7% from those given in Table 3. It is therefore reasonable to suggest that our assumption does not result in more than about 5% uncertainty in the derived dissociation constants.

Several approximations are needed to get constant α values, whence the dissociation constants can be calculated :

$$K = [M^{++}][R^-]f_1f_2/[MR^+]f_3 = (1 - \alpha)(2 - \alpha)cf_1f_2/2\alpha f_3$$

the simple Debye–Hückel activity coefficient expression, $-\log f_i = 0{\cdot}509z_i^2I^{\frac{1}{2}}$ in which z_i is the ion valency, being used. The values of Λ^0 and b are given in Table 1. Tables 2 and 3 give the conductivities and the values of α and K for the glycollates and lactates, respectively.

TABLE 3. *Conductivities of lactates.*

Run	10^4c	Λ	10^4I	$10^3\alpha$	10^3K	Run	10^4c	Λ	10^4I	$10^3\alpha$	10^3K
		Nickel						Zinc			
2	13·461	75·65	18·18	14·84	5·86	1	6·126	80·01	8·69	8·22	5·72
1	13·852	75·52	18·70	14·95	5·96	1	8·537	78·14	11·90	10·54	5·84
2	20·067	72·48	26·39	18·88	6·15	2	9·200	77·64	12·78	11·19	5·83
1	26·833	69·80	34·52	22·48	6·24	2	10·647	76·66	14·64	12·46	5·86
2	27·764	69·33	35·21	23·19	6·15	1	12·927	75·08	17·50	14·62	5·75
3	30·658	68·36	38·48	24·49	6·20	2	13·494	74·87	18·24	14·83	5·87
2	36·056	66·46	44·24	27·21	6·10	1	19·288	71·43	25·13	19·72	5·60
1	38·737	65·75	47·27	28·16	6·15	2	20·089	71·28	26·16	19·78	5·78
3	54·666	61·44	63·21	34·43	5·94	2	26·494	68·37	33·39	23·98	5·64
		Cadmium						Manganese			
1	10·445	81·01	15·26	3·99	20·5	2	10·759	82·23	15·92	2·18	39·4
2	11·178	80·69	16·29	4·29	20·2	1	12·277	81·65	18·11	2·68	36·0
2	15·412	79·16	22·27	5·56	20·4	2	15·504	80·76	22·77	3·08	38·4
1	15·523	79·04	22·38	5·76	19·8	1	15·995	80·55	23·48	3·30	36·7
1	19·321	77·86	27·68	6·76	20·1	2	18·444	79·94	27·02	3·62	37·8
2	21·919	77·05	31·20	7·54	19·9	1	22·358	78·88	32·54	4·42	36·2
1	28·076	75·50	39·65	8·87	20·5	2	26·076	78·09	37·85	4·88	37·2
2	34·484	73·93	48·11	10·43	20·3	1	29·550	77·32	42·70	5·43	36·8
1	36·078	73·63	50·26	10·66	20·3						
				Sodium							
2	5·308	83·81	—	—	—	2	24·65	81·81	—	—	—
2	11·688	83·00	—	—	—	1	27·62	81·62	—	—	—
1	12·633	82·83	—	—	—	2	37·58	80·96	—	—	—
1	17·55	82·37	—	—	—	1	40·81	80·85	—	—	—
2	18·73	82·27	—	—	—	3	71·86	79·39	—	—	—

The cobalt salts could not be conveniently investigated by direct measurements since they are too soluble to provide crystals for weighing, and the precise determination of cobalt is somewhat difficult. Instead, the specific conductivities of mixtures of cobalt chloride and sodium glycollate or lactate were measured, and the differences between the observed measurements and those calculated on the assumption that dissociation is complete were used to estimate the concentrations of CoR^+. This method has been applied to some inorganic salts (Jones, Monk, and Davies, *loc. cit.*). If c_1 is the equivalent concentration of sodium salt, c_2 is that of the cobalt chloride, and β that of CoR^+, then since

$$10^3\kappa \text{ (obs.)} = 10^3\Sigma\kappa_i = \Sigma\lambda_ic_i$$

where κ represents specific conductivity, then

$$10^3\kappa \text{ (obs.)} = \lambda_{Na}c_1 + 2\lambda_{Co}(c_2/2 - \beta) + \lambda_{Cl}c_2 + \lambda_R(c_1 - \beta) + \lambda_{CoR}(\beta)$$

and if ionisation were complete,

$$10^3\kappa \text{ (theor.)} = \Sigma(\lambda^0_i - b_iI^{\frac{1}{2}}) = \lambda_{Na}c_1 + 2\lambda_{Co}c_2/2 + \lambda_{Cl}c_2 + \lambda_Rc_1$$

whence, by assuming $\lambda^0_{CoR} = 0{\cdot}5\lambda^0_{Co}$,

$$\beta = 10^3\{\kappa \text{ (theor.)} - \kappa \text{ (obs.)}\}/\{\lambda_R + 1{\cdot}5\lambda_{Co}\}$$

β is obtained by approximations, by using $I = (c_1 + 1{\cdot}5c_2 - 2\beta)$. In the calculation of b_i in the Onsager equations, the valency product terms have been based on the sodium salt and on cobalt chloride. Table 4 contains the measurements and calculations, $\Lambda^0 = 129{\cdot}6$ being used for cobalt chloride (unpublished work—the data indicate complete ionisation).

Lead lactate has been similarly treated by the mixture method since this salt could not be crystallised. Sodium lactate and lead chloride were used. The latter has a dissociation constant of 0·03 (Righellato and Davies, *loc. cit.*), so that a correction for $PbCl^+$ was necessary. This practically cancels out in the observed and theoretical expressions for κ, and its main

TABLE 4. *Conductivities of cobalt chloride and sodium glycollate or lactate.*

10^4c_1	10^4c_2	$10^4\kappa$ (obs.)	$10^4\kappa$ (theor.)	$10^5\beta$	10^3I	10^3K	10^4c_1	10^4c_2	$10^4\kappa$ (obs.)	$10^4\kappa$ (theor.)	$10^5\beta$	10^3I	10^3K
Glycollate							Lactate						
18·810	12·651	3·0642	3·1499	7·72	3·624	9·8	26·430	4·706	2·6794	2·7132	3·18	3·286	12·7
18·728	17·324	3·5811	3·6879	9·70	4·278	10·4	26·308	9·637	3·2144	3·2838	6·58	3·945	12·1
18·611	24·105	4·3254	4·4598	12·3	5·229	10·9	26·080	18·974	4·2212	4·3467	11·7	5·219	12·6
10·376	15·516	2·7257	2·7801	4·90	3·255	11·2	25·883	26·978	5·0820	5·2438	15·8	6·321	12·6
24·749	14·859	3·7864	3·9001	10·3	4·498	10·8	7·256	16·784	2·5965	2·6296	3·10	3·180	13·9
							19·560	16·154	3·4325	3·5178	8·12	4·217	12·4
							46·451	14·776	5·2745	5·4205	14·3	6·577	12·8

influence is in correcting the lead-ion concentration in the expression for K, and in the value of I. Table 5 contains the data, where γ represents the $PbCl^+$ concentrations. For lead chloride, $\Lambda^0 = 147{\cdot}0$ was used (Norman and Garrett, *J. Amer. Chem. Soc.*, 1947, **69**, 110).

TABLE 5. *Conductivity of lead chloride and sodium lactate solutions.*

10^4c_1	10^4c_2	$10^5\beta$	$10^5\gamma$	$10^4\kappa$ (obs.)	$10^4\kappa$ (theor.)	10^4I	10^3K
3·919	2·889	1·42	2·44	0·7093	0·7429	5·569	1·59
5·894	2·874	1·37	3·18	0·8593	0·9028	7·386	1·71
8·333	2·854	1·35	3·99	1·0451	1·0995	9·652	1·74
8·277	7·432	8·67	9·76	1·6053	1·7407	11·73	1·74
5·764	3·651	2·21	3·79	0·9507	1·0026	7·748	1·77
5·746	5·798	5·47	6·05	1·2237	1·3200	8·778	1·65
5·722	8·598	11·7	9·18	1·5764	1·7014	10·10	1·47

The cupric salts had been studied by using the solubility of cupric iodate in solutions of NaR (Lloyd, Wycherley, and Monk, *loc. cit.*). The results suggested that both CuR^+ and CuR_2 are formed, so some fresh measurements were made, and this was confirmed. To calculate both K_1 and K_2 the same method of approximations was used, except that in deriving the amounts of CuR_2, values of K_1 were tried until K_2 remained constant over a concentration range, *i.e.*, the concentrations of CuR^+ were calculated from

$$\log [CuR^+] = \log [Cu^{++}][R^-] - \log K_1 - 2\phi(I)$$

The results are given in Table 6, the solubility in water being taken as $3{\cdot}26 \times 10^{-3}$ M at 25°. Keefer (*J. Amer. Chem. Soc.*, 1948, **70**, 476) reports the very close figure of $3{\cdot}245 \times 10^{-3}$, but in

TABLE 6. *Solubility of cupric iodate in sodium glycollate and lactate.*

(Concentrations $\times 10^3$.)

	Glycollate ($10^3K_1 = 1{\cdot}28$)			Lactate ($10^3K_1 = 0{\cdot}95$)		
Solubility	6·45	7·36	8·99	6·34	7·70	8·83
Sodium salt	15·12	20·16	30·17	12·69	19·04	25·38
$[Cu^{++}]$	1·07	$0{\cdot}88_5$	0·67	1·06	0·79	0·65
$[R^-]$	8·41	11·58	18·36	6·26	9·67	14·03
$[CuR^+]$	3·95	4·28	4·75	4·03	4·37	4·93
$[CuR_2]$	1·38	2·15	3·53	1·20	2·50	3·21
10^3I	22·29	27·07	36·85	19·91	25·74	32·20
10^3K_2	1·80	1·69	1·73	1·60	1·24	1·54

previous work (Lloyd, Wycherley, and Monk, *loc. cit.*) $3{\cdot}33 \times 10^{-3}$ was constantly obtained. The crystals used in obtaining this higher figure were freshly prepared, whereas those used for the present work had been aged for some months, which may explain the difference.

DISCUSSION

A summary of the average pK values obtained in the present work together with some from other sources is given in Table 7. Except for copper and possibly magnesium, the pK's of the glycollates are larger than those of the lactates. The pK order of many copper

salts has been previously explained in terms of induction effects (Lloyd, Wycherley, and Monk, *loc. cit.*), and the electron-displacing ability of the methyl group which accounts for the pK of lactic acid being greater than that of glycollic acid (3·862 and 3·831 at 25° respectively; Harned and Owen, *op. cit.*, p. 580) similarly explains the order of their copper salts. With metals of lower ionisation potential, the overall anion size is generally more important than induction effects (Colman-Porter and Monk, *loc. cit.*) so the pK order of the magnesium salts should be glycollate > lactate. It is noticeable that the pK's of magnesium acetate and propionate are also in the reverse order to the anion size (Cannan and Kibrick, *J. Amer. Chem. Soc.*, 1938, **60**, 2314). The smallness of the magnesium ion may be the reason for this behaviour as it may limit the distance of anion approach; this is referred to on p. **550**. Although this does not in itself explain why the larger lactate ion seems to bind slightly more than does the glycollate, yet it may explain why the pK's of this salt are smaller than one would expect from the values of the other alkaline earths, and taken in conjunction with this, the methyl group, in displacing the electrical centre of the

FIG. 1.

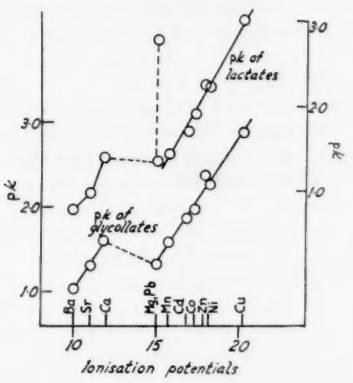
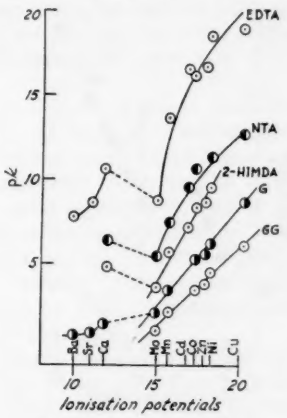


FIG. 2.



See Table 8 for legends.

carboxylate group nearer to the anion surface, reduces the effective distance of closest approach.

The variations found in any one series on changing the cation have been discussed in several papers. Irving and Williams (*Nature*, 1948, **162**, 746) and Calvin and Melchior

TABLE 7. *Average* pK*'s, ionisation potentials, and cation radii.*

	Ca	Sr	Ba	Mg	Mn	Cd	Co	Zn	Pb	Ni	Cu
pK (Glycollates)	1·59[a]	1·31[b]	1·04[b]	1·33[b]	1·582	1·866	1·975	2·376	—	2·261	2·89 (K_1), 1·77 (K_2)
pK (Lactates)	1·47[a]	0·96[b]	0·77[b]	1·34[b]	1·428	1·695	1·896	2·239	2·777	2·216	3·02 (K_1), 1·82 (K_2)
2nd Ionisation potls. (ev)[c]	11·82	10·98	9·95	14·96	15·70	16·84	17·3	17·89	14·96	18·2	20·2
Cryst. cation radii (Å)[d]	0·99	1·13	1·35	0·65	0·80	0·97	0·72	0·74	1·21	0·70	0·72[e]
λ^0 (cations)	59·50[f]	59·46[f]	63·64[f]	53·06[f]	53·05[g]	52·7[g]	53·5[h]	52·8[g]	70·7[i]	53·7[g]	53·9[j]
Hydrated cation radii (Å)	3·08	3·08	2·88	3·45	3·45	3·48	3·43	3·47	2·59	3·41	3·40

[a] Davies, *J.*, 1938, 277. [b] Colman-Porter and Monk, *loc. cit.* [c] Latimer, "Oxidation Potentials," Prentice-Hall, 1938, p. 14. [d] Pauling, "Nature of the Chemical Bond," Cornell, 1939, p. 346. [e] Ahrens, *Nature*, 1952, **169**, 463. [f] Harned and Owen, *op. cit.*, p. 172. [g] See Table 1. [h] Unpublished work. [i] Norman and Garrett, *loc. cit.* [j] Owen and Gurry, *J. Amer. Chem. Soc.*, 1938, **60**, 3074.

(*J. Amer. Chem. Soc.*, 1948, **70**, 3270) suggested that the pK values of several complexes appear to be related to the ionisation potentials of the metals. Previous limited data pointed to magnesium's being an exception to this (Colman-Porter and Monk, *loc. cit.*), and

Williams (*loc. cit.*), considering the Group IIA metals, suggested reasons for the low stability of many magnesium salts (see p. 550). Van Eck (*Rec. Trav. chim.*, **1953**, **72**, 50) examined the complexes formed between numerous ligands and up to nine cations. Many of these obey a linear relationship when pK is plotted against the second ionisation potential of the metals, and magnesium does not appear to be anomalous in this scheme. On the other hand, lead and sometimes zinc do not conform. In Fig. 1, the pK data from Table 7 for the lactates and glycollates are plotted against the second ionisation potentials. Again, lead is well out of position, but magnesium fits in fairly well. The plots are not strictly linear, and the other three alkaline earths lie on a separate curve. To compare these salts with some others, further complexes (Table 8) are plotted in Fig. 2. A fairly smooth curve can be drawn from magnesium to copper in all cases, but once more calcium, strontium, and barium have their separate curve, and again lead (not plotted) is unique. The features therefore appear to be general, and as a useful working rule, if the pK values of, say, magnesium and copper are known, those of manganese, cadmium, cobalt, zinc, and nickel can be predicted with reasonable accuracy. Ferrous complexes (iron = 16·15 ev)

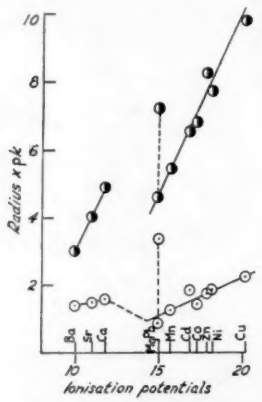


FIG. 3.

⊙ = Crystal radii, ◑ = radii of hydrated ions (Å).
Plots of lactates.

should also fit into this scheme, and for the two cases examined, this seems to be so. These are ethylenediaminetetra-acetic acid (see Table 8) and acetylacetone (Vitert, Fernelius, and Douglas, *J. Amer. Chem. Soc.*, **1953**, **75**, 2741). The latter data show some scatter, but this may be due to neglect of the incomplete dissociation of the inorganic salts used. The general method of determining the pK's of complexes is to make pH titrations with sodium

TABLE 8. pK *Values of some complexes.**

	Ca	Sr	Ba	Mg	Mn	Cd	Co	Zn	Pb	Ni	Cu
NTA	6·4	—	—	5·4	7·4	9·5	10·6	10·4	11·8	11·3	12·7
2-HIMDA	4·8	—	—	3·5	5·6	7·1	8·3	8·6	9·5	9·5	—
EDTA	10·6	8·6	7·8	8·7	13·5	16·5	16·1	16·6	18·2	18·5	18·4
G	1·43	0·91	0·77	2·07	3·44	—	5·23	5·52	5·27	6·18	8·62
GG	1·24	—	—	1·06	2·15	—	3·49	3·80	3·23	4·49	6·04

* NTA = Nitrilotriacetic acid (Schwarzenbach, Ackermann, and Ruckstuhl, *Helv. Chim. Acta*, 1949, **32**, 1175; Schwarzenbach and Freitag, *ibid.*, 1951, **34**, 1492). 2-HIMDA = 2-Hydroxyethyliminodiacetic acid (Chaberek, Courtney, and Martell, *J. Amer. Chem. Soc.*, 1952, **74**, 5057). EDTA = Ethylenediaminetetra-acetic acid (Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798; Schwarzenbach and Freitag, *ibid.*, 1951, **34**, 576; Schwarzenbach and Heller, *ibid.*, p. 576). G = Glycine, GG = glycylglycine (Monk, *Trans. Faraday Soc.*, 1951, **47**, 297; Colman-Porter and Monk, *loc. cit.*).

hydroxide of inorganic salt-chelating agent mixtures, and sometimes, to overcome solubility difficulties, mixed solvents are used. The ion-association of the inorganic salts is not taken into account, and this may be considerable, especially in mixed solvents. Vitert *et al.* (*loc. cit.*), for instance, obtained different pK's when using chlorides, nitrates, and

perchlorates in mixed solvents, and recognised that the incomplete dissociation of these salts was the probable reason. These authors incidentally (*loc. cit.*, p. 2736) tried plotting pK's against the metal-ion negativities : there is fairly good correspondence, but beryllium, cadmium, and copper are out of line.

The four ions that do not fit in with the main curves of the pK plots of Fig. 1 are relatively large when unhydrated, but are smaller than the others in their hydrated forms. To get some idea of the sizes of the hydrated cations, values (Table 7) have been calculated by means of Stokes's law from the limiting cation mobilities (see Jenkins and Monk, *loc. cit.*). This is admittedly not very accurate, but it serves to give some comparative figures. In general, one would expect pK values to be related to the ion sizes, as well as to the other factors, and to examine this the products of the pK's and both hydrated and unhydrated cation radii are plotted in Fig. 3 against the ionisation potentials (the lactate series has been taken for this). Use of the unhydrated radii seems to show the more promise, but it still does not bring lead into line. Apart from this exception, the inference that interaction involves the bare cations would also seem to receive further support from the hydroxides. Davies (*J.*, 1951, 1256) has shown that the pK's of many hydroxides are related to the bare cation sizes, and Van Eck (*loc. cit.*) has shown that numerous hydroxides fit into the ionisation potential scheme. A fairly regular curve is produced if one plots the product of the pK's and the bare radii against the potentials, thallium and silver being exceptions.

However, one is still forced to recognise that even with this method the lower plot of Fig. 3 for the lactates is in two main parts as in Fig. 1. If magnesium and manganese had larger radii a fairly general curve could be drawn (omitting lead), which brings us back to Williams's suggestion (*loc. cit.*) that the cation size can limit the extent to which anions can approach the small magnesium ion owing to the anion repulsion forces that are set up when the anions are brought into close proximity in the cation neighbourhood. If this is so, the effective radius of the magnesium ion is somewhat greater than the crystallographic value. The same would have to apply, though to a smaller extent, to manganese. On the other hand, the manganese ion is in fact slightly larger than those of zinc and nickel, for instance, so one is by no means certain that this is correct.

The present picture is therefore not entirely satisfactory. Although general features are apparent, the number of exceptions to the various relationships that have been tried indicates that more fundamental principles are involved than those so far considered. A more detailed analysis of the nature of the valency forces may improve the position.

THE EDWARD DAVIES CHEMICAL LABORATORIES,
UNIVERSITY COLLEGE OF WALES, ABERYSTWYTH. [*Received, August 22nd,* 1953.]

The Preparation and Some Properties of Plutonium Fluorides.

By J. K. Dawson, (Miss) R. M. Elliott, R. Hurst, and A. E. Truswell.

[Reprint Order No. 4624.]

The milligram-scale preparation of plutonium trifluoride, tetrafluoride, and possibly two hydroxyfluorides by the reaction of hydrogen fluoride with plutonium dioxide or oxalate is described.

Precipitation of plutonium tetrafluoride from dilute aqueous solution gives a hydrate with the molecular weight of $2PuF_4,5H_2O$; vacuum dehydration of the precipitate at 300° gives plutonium trifluoride. When plutonium trifluoride is precipitated, sufficient water is trapped in the lattice to give material of composition $4PuF_3,3H_2O$. Thermogravimetric curves are described for the anhydrous fluorides and the precipitated fluorides.

The reaction of plutonium trifluoride with very dry oxygen has been studied, and by measurement of the oxygen pressure developed by the reverse reaction the free energy of formation of plutonium tetrafluoride has been deduced as 400 kcal./mole at 298° K.

Plutonium tetrafluoride undergoes disproportionation in vacuum at *ca.* 900° to give the trifluoride and probably the more volatile pentafluoride.

The main contribution to the dry chemistry of plutonium fluorides available in the literature is a paper by Fried and Davidson, who describe investigations into the reaction of plutonium trifluoride with very dry oxygen and into the vacuum decomposition of plutonium tetrafluoride ("The Transuranium Elements," McGraw-Hill Co., 1949, N.N.E.S. **14**, *B*, paper 6.11). The present communication describes more extensive investigations into these systems together with observations on the preparation of the fluorides and their reactions with water vapour.

Experimental

1. *The Thermo-balance.*—The thermogravimetric curves described below were obtained on a silica spring balance of sensitivity 1·30 mm./mg. using 5—30 mg. of material. The samples were supported in a platinum boat on the end of a long extension fibre so that the silica spring was well above the heated zone around the sample. Weight changes were observed by following the movement of an index fibre with a cathetometer which could be read to 0·01 mm. A curve was plotted for the change of apparent weight of the empty platinum boat with increasing temperature and this was applied as a correction to the experiments with the plutonium compounds present.

When change of weight with temperature was being observed, the rate of rise of temperature was kept to about 3°/min.

2. *Preparation of Plutonium Fluorides by Hydrofluorination.*—Hydrated plutonium tetraoxalate, $Pu(C_2O_4)_2,6H_2O$, was precipitated from an aqueous solution of the tetranitrate by addition of oxalic acid crystals. After being centrifuged and washed with very dilute nitric acid, the precipitate was slurried into platinum boats for conversion into oxide or for direct fluorination in a nickel tube.

Conversion of the oxalate into oxide was performed by heating it in a stream of air to about 300°. A stream of anhydrous hydrogen fluoride from a cylinder could be passed through the tube, and oxygen could be added to the hydrogen fluoride either pure or as air. The amount normally added was about 5—10%, although this could be varied over wide limits without affecting the product. The preparations were performed up to the 10 mg. scale and the results are shown in Table 1; *X*-ray powder diffraction photographs were used to determine the product by comparison with Zachariasen's data (*op. cit.*, paper 20.5).

3. *Reduction of* PuF_4 *with Hydrogen or Sulphur Dioxide.*—The tetrafluoride (1—5 mg.) was heated for 1 hr. in a platinum boat inside a Pyrex tube, which was swept out by the reducing gas before heating was commenced. The nature of the product was determined from *X*-ray diffraction photographs and the results are quoted in Table 2.

4. *Precipitation of Plutonium Tetrafluoride from Aqueous Solution.*—(*a*) Aqueous hydrofluoric acid was added to a dilute solution of quadrivalent plutonium in 3N-nitric acid in a plastic

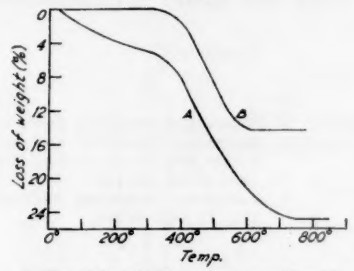
centrifuge tube. The pale pink precipitate was centrifuged, transferred to a glass tube, washed with ethanol, and dried at room temperature in a high vacuum.

TABLE 1. *The preparation of* PuF_3 *and* PuF_4.

Conditions	Temp.	Colour of product	Product	Conditions	Temp.	Colour of product	Product
Oxalate or	25°	Stone	Hydroxyfluoride (?)	Oxalate +	230°	Blue-purple	PuF_3
oxide +	100	,,	,,	HF	530	,,	PuF_3
HF	150	,,	,,		640	,,	PuF_3
					715	,,	PuF_3
Oxide +	450	V. pale pink	PuF_4		780	,,	PuF_3
HF +	530	Light brown	PuF_4				
oxygen	600	,,	PuF_4	Oxalate +	200	Cream	PuF_4
	640	,,	PuF_4	HF +	300	V. light brown	PuF_4
				oxygen	400	,,	PuF_4
PuF_3 +	450	Pink-brown	PuF_4		530	Light brown	PuF_4
HF +	530	Brown	PuF_4		600	,,	PuF_4
oxygen	630	,,	PuF_4				

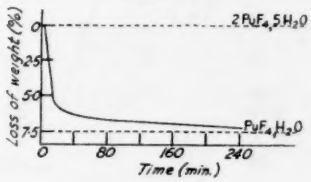
A 17·78 mg. sample was heated in air, and the thermogravimetric curve is shown in Fig. 1, where it is compared with a similar curve on a 12·71-mg. sample of anhydrous plutonium tetra-

FIG. 1.



A, Precipitated plutonium tetrafluoride.
B, Anhydrous plutonium tetrafluoride prepared by hydrofluorination of the dioxide.

FIG. 2.



fluoride prepared by hydrofluorination. The total weight change on the precipitated fluoride from room temperature to the final plateau (PuO_2 according to the *X*-ray diffraction pattern) was 24·9% (Calc. for $2PuF_4,5H_2O \longrightarrow 2PuO_2$: 24·75%).

(*b*) Small portions of the same fluoride precipitate (~200 μg.) were heated ***in vacuo*** and the composition of the product was determined from *X*-ray powder photographs (Table 3).

TABLE 2. *Reaction of* PuF_4 *with hydrogen and sulphur dioxide.*

$PuF_4 + H_2$				$PuF_4 + SO_2$			
Temp.	Product	Temp.	Product	Temp.	Product	Temp.	Product
100°	No reaction	230°	PuF_3	270°	No reaction	385°	$PuF_3 + PuF_4$
200	,,	300	PuF_3	300	$PuF_3 + PuF_4$	500	$PuF_3 + PuO_2$
220	,,						

TABLE 3. *The effect of vacuum heating on* $2PuF_4,5H_2O$.

Temp.	Pressure (mm. Hg)	Product
100°	10^{-4}	No change
200	10^{-4}	No *X*-ray diffraction pattern
300	10^{-5}	~90% PuF_3, ~10% PuO_2

(*c*) A sample of the fluoride precipitate (~30 mg.) was heated as in (*a*) at a uniform rate to 900° in a vacuum of 10^{-4} mm. Hg. No distinct plateaux were observed, but above 700° the slope of the weight–temperature curve increased considerably, and this was later seen to be due to sublimation of some material from the boat on to the surrounding silica tube. An *X*-ray diffraction photograph of the product showed it to be a mixture, PuF_3 ~80% + PuO_2 ~20%.

(*d*) A run similar to (*c*) was stopped at 550°, and the product found to be a PuF_3–PuF_4 mixture by *X*-ray diffraction photographs.

(*e*) The hydrated plutonium fluoride (22·62 mg.) was heated at 200° in a platinum boat suspended from the silica spiral, the system being pumped to 10^{-4} mm. Hg. The weight–time curve is shown in Fig. 2; after 200 min. the weight was still decreasing very slowly, the loss observed being 7·1% [Calc. for $2PuF_4,5H_2O \longrightarrow 2(PuF_4,H_2O)$: loss, 7·5%].

5. *Precipitation of Plutonium Trifluoride from Aqueous Solution.*—(*a*) Plutonium(IV) in dilute nitric acid solution was reduced to plutonium(III) by addition of hydroxylamine hydrochloride, and a precipitate was obtained on addition of aqueous hydrofluoric acid. The precipitate was centrifuged, washed twice with water, slurried from the plastic tube in which precipitation had taken place into a glass tube, washed with acetone, and dried at room temperature/10^{-5} mm.

On ignition in air, a 15·95 mg. sample of the dried precipitate gave the thermogravimetric curve shown in Fig. 3; the total weight loss from room temperature to the final PuO_2 plateau (confirmed as PuO_2 by *X*-ray diffraction and shown to have zero fluorine content by analysis) was 12·3%. Theoretical weight changes could be:

$$PuF_3,H_2O \longrightarrow PuO_2,\ 13{\cdot}69\% \qquad 2PuF_3,H_2O \longrightarrow 2PuO_2,\ 11{\cdot}15\%$$
$$4PuF_3,3H_2O \longrightarrow 4PuO_2,\ 12{\cdot}44\% \qquad PuF_3 \longrightarrow PuO_2,\ 8{\cdot}44\%$$

The precipitate gave a very diffuse *X*-ray diffraction pattern, closely related to that of anhydrous plutonium trifluoride. Small samples which were ignited to temperatures of 250°,

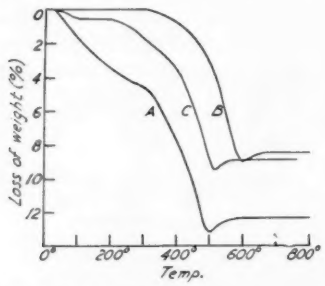


FIG. 3. *A, Precipitated plutonium trifluoride.*
B, Anhydrous plutonium trifluoride freshly prepared by hydrofluorination of the dioxide.
C, Anhydrous plutonium trifluoride after 12 days in air.

275°, and 320° showed the gradual fading of the *X*-ray diffraction lines without the appearance of any other pattern; at 400° the diffraction pattern was that of plutonium dioxide.

(*b*) Further thermogravimetric curves on other samples of precipitated plutonium trifluoride gave 12·25, 12·6, and 12·4% weight changes from room temperature to the PuO_2 plateau.

(*c*) For comparison, the thermogravimetric curve on a sample of anhydrous plutonium trifluoride (29·63 mg.) freshly prepared by hydrofluorination is shown also in Fig. 3. There was no detectable weight change below 300°; the total weight loss between this plateau and the final one beginning at *ca.* 700° (PuO_2) was 8·4% (Calc. for $PuF_3 \longrightarrow PuO_2$: 8·44%).

(*d*) A sample of anhydrous plutonium trifluoride (10·7 mg.), prepared in the same way as sample (*c*), was exposed to laboratory air for 12 days. The thermogravimetric curve then obtained is shown in Fig. 3. The weight change from the plateau at 100—200° to the final plateau was 8·32%, and the curve shows that the trifluoride adsorbed 0·6% of moisture from the atmosphere.

(*e*) A sample of anhydrous plutonium trifluoride prepared by dry hydrofluorination of PuO_2 was kept under dilute aqueous hydrofluoric acid for 3 days. After being washed with acetone and dried in high vacuum at room temperature, the compound gave a thermogravimetric curve very similar to that of the original trifluoride and had not taken up any water.

(*f*) Plutonium trifluoride was precipitated as in (*a*) except that the temperature of precipitation was 80°. The thermogravimetric curve on a 12·10 mg. sample then gave 10·1% loss of weight between room temperature and the plutonium dioxide plateau, *i.e.*, less water had been trapped in the trifluoride lattice than when precipitation was performed at a lower temperature.

6. (*a*) *Reaction of* PuF_3 *with Oxygen.*—As a result of initial experiments at 400—600° it was found necessary to perform a triple condensation of cylinder oxygen at liquid-nitrogen temperature in glass-bead-filled traps, followed by evaporation at liquid-oxygen temperature, in order to dry the gas sufficiently to prevent the formation of 100% PuO_2 as the reaction

product. The third trap, reaction tube, and trifluoride were pumped down to a vacuum of about 10^{-5} mm. Hg, and the trifluoride was degassed at 100° for several hours before admission of oxygen. The apparatus is shown in Fig. 4 together with the additions necessary for a study of the reverse reaction. The forward reactions were carried out for 30 min., and Table 4 gives a summary of the results obtained, the approximate proportions of the plutonium compounds in the products having been determined from *X*-ray powder diffraction photographs. An alternative method of estimating the relative amounts of PuF_4 and PuO_2 is shown in Table 5.

TABLE 4. *Reaction of* PuF_3 *with dry oxygen.*

Temp.	PuF_3 (mg.)	Product, % PuF_3	PuF_4	PuO_2	Temp.	PuF_3 (mg.)	Product, % PuF_3	PuF_4	PuO_2
400°	45	60	40		600°	48	—	60	40
500	50	—	60	40					

6. (*b*) *Reverse reaction.*—Initial experiments to measure the oxygen pressure developed by the reverse reaction failed owing to the production of pure PuO_2 instead of PuF_3. This was probably due to the absorption of water vapour during the removal of the reaction mixture (PuF_4 + PuO_2) from the apparatus in order to extract samples for analysis. Only a trace of water vapour would be required to set off a chain reaction at higher temperatures involving the walls of the

FIG. 4.

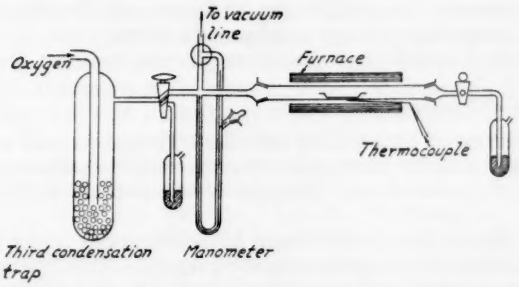
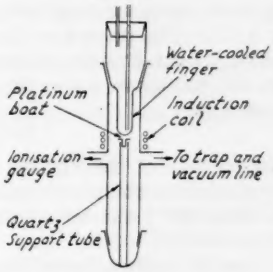


FIG. 5.



reaction tube, similar to the well-known decomposition of UF_4, *i.e.*, $PuF_4 + 2H_2O \longrightarrow PuO_2 + 4HF$; $SiO_2 + 4HF \longrightarrow SiF_4 + 2H_2O$. The only way in which this could be avoided was by performing both reactions in the same tube, and not taking out samples; as soon as the forward reaction was complete, the apparatus was re-evacuated overnight. The pressure was measured on a U-manometer (Fig. 4) containing a low vapour-pressure silicone oil of *d* 1·09. The oil was thoroughly degassed by warming during the preliminary evacuation of the apparatus, and pumping was continued on the vacuum-line side of the manometer during the actual pressure measurements. The results are given in Table 6.

7. *Disproportionation of Plutonium Tetrafluoride.*—The apparatus is shown in Fig. 5; PuF_4 was placed in the platinum boat and the apparatus was pumped down to 10^{-5} mm. Hg,

TABLE 5. *Magnetic susceptibilities at* 300° K *of the reaction product.*

Compound	$\chi_S \times 10^6$	Deduced composition of reaction product (%): PuF_4	PuO_2
Pure PuF_4	5·59	—	—
Pure PuO_2	2·69	—	—
Product of reaction at 600°	4·20	52	48
Product of reaction at 700°	4·54	64	36

TABLE 6. *The pressure of oxygen developed over a mixture of* PuF_4 *and* PuO_2.

Approx. composition of reaction mixture (%)		Temp.	Pressure developed	Approx. composition of reaction product (%)	
PuF_4	60	510°	Increased slowly for 7 hr., then remained constant for 1½ hr. at 7·2 mm.	PuF_3	70—80
PuO_2	40			PuO_2	30—20
PuF_4	60	800	Increased slowly for 3 hr., then remained constant for 2 hr. at 7·5 cm.	PuF_3	70—80
PuO_2	40			PuO_2	30—20

the tetrafluoride being degassed by warming to about 200°. An isolation tap was then closed, and heating to reaction temperature was commenced; the pressure measured by the ionisation gauge increased to $\sim 10^{-3}$ mm. Hg, but returned to its original value on cooling. The reaction conditions are given in Table 7. The residue in the boat was purple and was shown to be

TABLE 7. *Disproportionation of plutonium tetrafluoride.*

PuF_4 (mg.)	Heating time, min.	Temp.	Residue in boat	Deposit on finger
50	5	970°	PuF_3	Grey-brown
30	10	920	PuF_3	,, (~2 mg.)

PuF_3 by its *X*-ray diffraction pattern. About 2 mg. of light brown sublimate were scraped off the condensation finger; this material gave no *X*-ray diffraction pattern, but duplicate analyses on the 300—500-μg. scale, performed by air ignition to plutonium dioxide, gave 19·2 and 19·4% decrease in weight (theoretical values are: $PuF_3 \longrightarrow PuO_2$, 8·5%; $PuF_4 \longrightarrow PuO_2$, 14·0%; $PuF_5 \longrightarrow PuO_2$, 18·9%).

DISCUSSION

Dry Preparation of PuF_3 *and* PuF_4.—A suitable starting material for the preparation of the plutonium fluorides is the dioxide. The latter is obtained in various states of subdivision by the air ignition of many plutonium compounds; at one end of the scale is plutonium hydroxide, which gives a dense, rather unreactive oxide, and at the other end is the oxalate, $Pu(C_2O_4)_2,6H_2O$, which may be precipitated from aqueous solution and gives a very fluffy oxide more suitable for subsequent conversion into halides (Westrum, *op. cit.*, paper 6.57). The present study shows that the oxalate can be fluorinated directly with gaseous hydrogen fluoride without forming the oxide as an intermediate compound.

On the milligram scale, the hydrofluorination of plutonium dioxide does not follow the course (1):

$$PuO_2 + 4HF \longrightarrow PuF_4 + 2H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The product of the reaction of excess of high-quality cylinder hydrogen fluoride with either plutonium dioxide or oxalate is actually plutonium trifluoride over the temperature range 250—750°; the tetrafluoride is produced only if oxygen is added to the hydrogen fluoride stream.

A possible explanation of these facts is that the hydrogen fluoride contains traces of a reducing impurity such as sulphur dioxide or hydrogen produced by reaction of the hydrogen fluoride with the metallic walls of the cylinder and the reaction vessel. Qualitative experiments to determine whether plutonium tetrafluoride is easily reduced by sulphur dioxide or by hydrogen were performed and the results are shown in Table 2. It appears that sulphur dioxide is not a good reducing agent for plutonium tetrafluoride and that the production of plutonium trifluoride from the dioxide is probably explained according to (2).

$$PuO_2 + 3HF + \tfrac{1}{2}H_2 \longrightarrow PuF_3 + 2H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It is possible to write an expression (3) for the production of plutonium trifluoride without postulating the presence of hydrogen, and the thermodynamic data given by Brewer (Brewer *et al.*, *op. cit.*, paper 6.40; Brewer, "The Chemistry and Metallurgy of Miscellaneous Materials: Thermodynamics," McGraw-Hill Co., 1949, N.N.E.S., **19**, *B*, paper 5) (Table 9) show that the free-energy change of this reaction is −5 kcal./mole at 298° K and +2·5 kcal./mole at 500° K. The reaction is thus thermodynamically possible, and in this respect is similar to reaction (1) which has a free-energy change of −1 kcal./mole at 500° K.

$$2PuO_2 + 6HF \longrightarrow 2PuF_3 + 3H_2O + \tfrac{1}{2}O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Since the hydrogen will certainly be present owing to the reasons given above, reaction (2) seems the most probable one to represent the experimental conditions.

Between room temperature and 150° reactions (1), (2), and (3) do not apply. We have obtained two distinct compounds other than the simple fluorides in this temperature range; possibly they are hydroxyfluorides of the type $Pu(OH)_2F_2$ or $Pu(OH)F_3$ which might be expected to be intermediates in the formation of PuF_4 from PuO_2. It is hoped to investigate further the composition and reactions of these low temperature products; they are readily converted into plutonium trifluoride in a stream of hydrogen fluoride and

hydrogen, or into the tetrafluoride in a stream of hydrogen fluoride and oxygen by raising the temperature above 200°.

Precipitation of the Fluorides from Aqueous Solution.—It is reported that uranium tetrafluoride, precipitated from aqueous solution by the addition of aqueous hydrofluoric acid, takes the form of a hydrate, $2UF_4,5H_2O$, and that the main part of the water of crystallisation is removed in vacuum at 200° (Grosse, quoted in "The Chemistry of Uranium," McGraw-Hill Co., 1949, N.N.E.S., **5**, 360). The present experiments show that a similar hydrate is obtained with plutonium, and since anhydrous plutonium tetrafluoride is stable to moisture up to 300° (Fig. 1), it was supposed that heating the hydrate in vacuum to 200° might give the anhydrous tetrafluoride by analogy with uranium. According to Fig. 2, the precipitated hydrate under these conditions affords a compound having the molecular weight of PuF_4,H_2O (in such a condition that it gave a blank *X*-ray diffraction photograph). At higher temperatures the product of the vacuum dehydration is plutonium trifluoride. This rather surprising result might be accounted for by assuming that some of the water liberated from the crystals reacts with the tetrafluoride to produce plutonium dioxide and this dioxide reacts with more tetrafluoride according to (4):

$$PuF_4 + 2H_2O \longrightarrow PuO_2 + 4HF$$
$$3PuF_4 + PuO_2 \longrightarrow 4PuF_3 + O_2 \quad \ldots\ldots\ldots\ldots \quad (4)$$

$$4PuF_4 + 2H_2O \longrightarrow 4PuF_3 + 4HF + O_2 \quad \ldots\ldots\ldots \quad (5)$$

By using the free energies of formation taken from Table 9, reaction (5) may be calculated to have a free-energy change of +14 kcal. at 500° K and −17 kcal. at 1000° K. At the temperature of the experiments, the equilibrium pressure developed by the reaction may be calculated to be $\sim 10^{-3}$ mm. Hg, and pumping the system to 10^{-4} mm. Hg would help the attainment of the right-hand side of equation (5). The product was found to be contaminated with a small percentage of plutonium dioxide.

The thermogravimetric curves obtained on samples of the trifluoride precipitated at room temperature from aqueous solution and dried at room temperature in a high vacuum are different from those obtained by using trifluoride prepared by high-temperature hydrofluorination (Fig. 3, curves *A* and *B*). According to the weight change observed on ignition to plutonium dioxide, the precipitate contained three-quarters of a molecule of water of crystallisation per plutonium atom. Heating this material in vacuum to about 300° produces the anhydrous fluoride but the change is not reversible. This is shown by the fact that trifluoride prepared in the dry way and kept in contact with dilute aqueous hydrofluoric acid for several days still gave the thermogravimetric curve for the anhydrous salt; also from an experiment in which the precipitated trifluoride was heated in a sealed tube, one end being cooled so that drops of water condensed there, and on standing at room temperature there was no evidence of the water's recombining with the plutonium trifluoride.

The *X*-ray diffraction pattern of the precipitated plutonium trifluoride was very diffuse but the spacings appeared to be the same as in the anhydrous salt. It is difficult to see how the water could be accommodated in the trifluoride lattice unless it were to be trapped between layers of fluorine atoms, giving rise to *X*-ray line intensity variations which we would not have observed owing to the diffuse nature of the films (for the structure of anhydrous plutonium trifluoride, see Zachariasen, *op. cit.*). The precipitate is probably not a definite complex since it begins to lose weight as soon as the temperature is raised, and the amount of water it contains varies with the temperature of precipitation.

These results may mean that a small correction will be necessary to Westrum and Eyring's calorimetric measurement of the heat of formation of plutonium trifluoride ("The Transuranium Elements," McGraw-Hill Co., 1949, N.N.E.S. **14**, *B*, paper 6.52). This was obtained by observation of the heat of precipitation from aqueous solution on the assumption that the precipitate is the anhydrous compound.

The troughs obtained on the plutonium trifluoride thermogravimetric curves at 500—600° were not observed with other plutonium compounds. The weight increases from the troughs to the plutonium dioxide plateaux were somewhat variable, the maximum observed corresponding to the possible existence of $PuO_{1.75}$. Attempts to isolate this phase were

not successful, probably owing to rapid conversion into the dioxide as the sample temperature was being lowered.

Reaction of PuF_3 *with Oxygen.*—Fried and Davidson (*loc. cit.*) found that the reaction of very dry oxygen with PuF_3 at 600° did not produce PuO_2 (as had been reported previously) but rather a mixture of PuF_4 (~60%) and PuO_2 (~40%). Since they obtained PuF_3 by heating this mixture in vacuum, they postulated the reversible reaction:

$$4PuF_3 + O_2 \underset{\text{Vacuum}}{\overset{600°}{\rightleftharpoons}} 3PuF_4 + PuO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Confirmation of the relative proportions of PuF_4 and PuO_2 formed in the forward reaction was obtained by the present authors from *X*-ray diffraction data (Table 4). The magnetic susceptibilities of pure PuF_4 and pure PuO_2 have been measured recently (Dawson, *J.*, 1952, 1882) and this suggested an alternative means of analysing this reaction product, the magnetic susceptibility of a mixture being directly dependent on the ratio of its components. The deduced composition of the reaction product (Table 5) was in agreement with that obtained from the *X*-ray photographs; both methods show rather more PuO_2 than the 25% to be expected from reaction (6), but this could easily be accounted for by residual water vapour in the apparatus.

From the data of Table 6 and by the use of the relation $\Delta F = \boldsymbol{R}T \ln p(O_2)$, the free-energy change for the reverse of equation (6) was calculated to give the values shown in Table 8, which also gives values at other useful temperatures obtained by extrapolation and interpolation.

TABLE 8. *The free-energy change for the reverse of reaction* (6).

Temp. (° K)	298	500	783	1000	1073
ΔF, kcal.	14·8	12·2	11·3	10·6 *	10·4

* This value was interpolated; the others were extrapolated.

The free energies of formation of PuF_3 and PuO_2, taken from tables of $(\Delta F - H_{298})/T$ by Brewer (*op. cit.*), are given in Table 9, together with values for HF and H_2O required in other sections of this paper. These values being used in conjunction with the data of Table 8, the free energy of formation of PuF_4 was calculated to have the values given in the last column of Table 9.

TABLE 9. *Free energies of formation,* ΔF *(in kcal./mole).*

Temp. (° K)	PuF_3	PuO_2	HF	H_2O	PuF_4	Temp. (° K)	PuF_3	PuO_2	HF	H_2O	PuF_4
298°	356	238·2	64·9	54·6	400	1000°	315	210	65·8	46·0	353·5
500	344·5	230	65·2	52·4	387						

Disproportionation of Plutonium Tetrafluoride.—It was reported by Fried and Davidson (*loc. cit.*) that if plutonium tetrafluoride was heated in vacuum to about 900°, a residue of plutonium trifluoride was formed and a sublimate of trifluoride could be collected on a cold finger. There are two possible mechanisms by which these facts might be explained; either by the direct reaction (7) or by the successive reactions (8) and (9). They suggested that reaction (9) took place on the cold finger:

$$PuF_4 \longrightarrow PuF_3 + \tfrac{1}{2}F_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$2PuF_4 \longrightarrow PuF_3 + PuF_5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$PuF_5 \longrightarrow PuF_3 + F_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

We have confirmed that plutonium trifluoride is in fact formed as a residue, but our sublimate was certainly not trifluoride. The colour was rather like that of the tetrafluoride, but evidence against its being PuF_4 was that it was readily soluble in 6N-nitric acid (the original PuF_4 was not), and ignition to PuO_2 in air gave a weight change corresponding to PuF_5. The sublimate appeared to be stable in air although by analogy with UF_5 it would easily be hydrolysed.

The authors thank Drs. J. S. Anderson and J. Milsted for helpful discussions, and the Director, A.E.R.E., for permission to publish this paper.

A.E.R.E., HARWELL, NR. DIDCOT, BERKS. [*Received, August 20th,* 1953.]

The Chemistry of Plant-growth Regulators. Part I. 2 : 4-Dichloro-6-hydroxyphenoxyacetic Acid and Related Compounds.

By G. W. K. Cavill and D. L. Ford.

[Reprint Order No. 4727.]

Synthesis of 2 : 4-dichloro-6-hydroxyphenoxyacetic acid and of its methyl ether is described. The lack of growth-regulating properties of these compounds is briefly discussed in relation to some current theories of the mode of action of 2 : 4-dichlorophenoxyacetic acid (2 : 4-D). The direct nitration of 2 : 4-D is re-investigated.

Aryloxyalkanecarboxylic acids are important synthetic plant growth-regulators, particularly 2 : 4-di- and 2 : 4 : 5-tri-chlorophenoxyacetic acids. However, when chlorine or bromine is substituted in both the 2- and the 6-position, as in 2 : 6-di- and 2 : 4 : 6-trichlorophenoxyacetic acid, activity is lost. This apparent necessity for one free *ortho*-position has led to numerous hypotheses. Muir *et al.* (*Plant Physiol.*, 1949, **24**, 359; 1951, **26**, 369) suggested that 2 : 4-dichlorophenoxyacetic acid (2 : 4-D) reacts with a plant substrate in the *ortho*-position, Leaper and Bishop (*Bot. Gazz.*, 1951, **112**, 250) postulated oxidation to a *p*-quinone, and Holly, Boyle, and Hand (*Arch. Biochem.*, 1950, **27**, 143) believe nuclear hydroxylation (position unspecified) may occur during the metabolism of 2 : 4-D.

The synthesis of 2 : 4-dichloro-6-hydroxyphenoxyacetic acid is now reported and the preliminary testing of this compound discussed in relation to the above hypotheses.

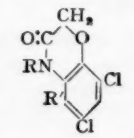
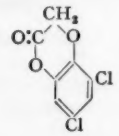
Although synthesis *via* 2 : 4-dichloro-6-nitrophenoxyacetic acid has not proved possible, it has led to an investigation of the nitration of 2 : 4-D. 2 : 4-Dichloro-6-nitrophenol could not be converted into the phenoxyacetic acid by known procedures (cf. Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2191). Ultimately the sodium salt of the phenol was condensed with *n*-butyl chloroacetate in diethylene glycol, to give *n*-butyl 2 : 4-dichloro-6-nitrophenoxyacetate. Direct nitration of 2 : 4-D has been stated to give only 5-nitro-acid (Mahler, Speer, and Roberts, *Science*, 1949, **110**, 562; Wolfe, Wood, Klipp, Fontaine, and Mitchell, *J. Org. Chem.*, 1949, **14**, 900); our nitration with an excess of cold concentrated mixed acid gave largely the 5-nitro-acid, together with the 5 : 6-dinitro-acid and a small yield of the 6-nitro-acid.

The structure of the 6-nitro-compound was proved by reduction with ferrous hydroxide to the cyclic lactam (I; R = R′ = H) [cf. Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 1435) for reduction of *o*-nitrophenoxyacetic acid], which could not be hydrolysed to 6-amino-2 : 4-dichlorophenoxyacetic acid. Reduction of *n*-butyl 2 : 4-dichloro-6-nitrophenoxyacetate with hydrogen in the presence of Raney nickel also gave the lactam, butanol being eliminated. In contrast, hydrogenation with a palladium–charcoal catalyst gave a product, $C_8H_5O_3NCl_2$, containing one extra oxygen atom. This compound, soluble in concentrated sodium hydroxide solution (being immediately reprecipitated on addition of mineral acid) and insoluble in sodium hydrogen carbonate solution, reduces hot Fehling's solution but does not react with ammoniacal silver nitrate solution. It gives an intense wine red colour with alcoholic ferric chloride solution characteristic of hydroxamic acids and forms an apple-green copper derivative on treatment with cupric acetate in alcohol. Confirmation of the cyclic hydroxamic acid structure (I; R = OH; R′ = H) is afforded by reduction with zinc and hydrochloric acid to the lactam (I; R = R′ = H). Reduction with zinc in acetic acid gives both the lactam and the hydroxamic acid; in sulphuric acid it gives only the lactam.

The ready formation of insoluble lactams has been used to prove the structure of the 5 : 6-dinitro-acid. This acid is also formed on nitration of 2 : 4-dichloro-5-nitrophenoxyacetic acid, and as it is reduced with zinc and hydrochloric acid to a lactam (I; R = H, R′ = NH_2), the second nitro-group is in position 6.

An alternative route to 2 : 4-dichloro-6-hydroxyphenoxyacetic acid starting from 3 : 5-dichlorocatechol was next investigated. The 2-hydroxyl group of the dichlorocatechol

should be the more acidic, hence the catechol was converted into a monosodium salt and treated with ethyl chloroacetate. Only one monohydroxydichlorophenoxyacetate was isolated, together with 3 : 5-dichloro-1 : 2-di(ethoxycarbonylmethoxy)benzene and some unchanged dichlorocatechol. The dichlorohydroxyphenoxyacetic acid, obtained on hydrolysis of the ester, gives a light blue colour with alcoholic ferric chloride solution and couples

(I)  (II) 

with diazotised sulphanilic acid. It gives a positive Gibb's test (pale blue) indicating that the *para*-position to the hydroxyl group is free, whilst additional evidence of an unsubstituted *ortho*-position (relative to hydroxyl) is given by nitration and reduction, the product not forming a lactam. The hydroxy-derivative is thus the required 2 : 4-dichloro-6-hydroxyphenoxyacetic acid, and was characterised as the methyl ether and by cyclisation to the lactone (II).

Preliminary testing for plant-growth-regulating properties by spraying of a 0·1% solution of sodium 6-hydroxy-2 : 4-dichlorophenoxyacetate on mature tomato plants gave no detectable activity whilst a 0·1% solution of 2 : 4-D showed extreme epinasty, twisting, and eventually death. No significant reduction in elongation of the primary maize root was observed with the 6-hydroxy- or 6-methoxy-2 : 4-dichlorophenoxyacetic acids, even at ten times the strength effective for 2 : 4-D. On the contrary there was a small but highly significant increase in root elongation over that shown by distilled-water controls. These results suggest that hydroxylation in position 6 is not an essential step in the production of an active metabolite from 2 : 4-D; whilst not conclusive, such observations also render the quinone hypothesis less likely. Wain [" Plant Growth Substances," Roy. Inst. Chem. (London), 1953] briefly records that 2 : 4-dichloro-6-fluorophenoxyacetic acid possesses high activity in the Went pea test, and such a result suggests that a free *ortho*-position may not be essential for activity in the aryloxyalkanecarboxylic acids.

Experimental

Nitration of 2 : 4-*Dichlorophenoxyacetic Acid.*—2 : 4-Dichlorophenoxyacetic acid (110·5 g., 0·5 mole) was dissolved in concentrated sulphuric acid (300 ml.) at 0—5° and concentrated nitric acid (50 ml.) was added during 30 min. with vigorous stirring. The amber mixture was poured on ice and the yellow solid, so precipitated, was filtered off, well washed with water, and air-dried. Fractional crystallisation from benzene–light petroleum (b. p. 60—80°) gave the 2 : 4-dichloro-5-nitrophenoxyacetic acid (97 g.) as pale yellow prisms, m. p. 158·5—159° (Found : C, 36·3; H, 1·85; N, 5·2. Calc. for $C_8H_5O_5NCl_2$: C, 36·1; H, 1·9; N, 5·3%), and some 2 : 4-dichloro-6-nitrophenoxyacetic acid (3·0 g.), m. p. 128° alone or mixed with the acid (m. p. 128—128·5°) prepared from 2 : 4-dichloro-6-nitrophenol. The residues from this crystallisation were taken up in aqueous ethanol; some esterification occurred and an ethyl ester separated as colourless needles (1·0 g.), m. p. 84—85°. Hydrolysis gave 2 : 4-*dichloro*-5 : 6-*dinitrophenoxyacetic acid*, small yellow prisms, m. p. 185° (from ethanol) (Found : C, 30·8; H, 1·45; N, 8·8. $C_8H_4O_7N_2Cl_2$ requires C, 30·85; H, 1·3; N, 9·0%). The mother-liquors on further crystallisation yielded *ethyl* 2 : 4-*dichloro*-5-*nitrophenoxyacetate*, colourless plates, m. p. 95—97° (from ethanol) (Found : C, 40·5; H, 3·0; N, 4·8. $C_{10}H_9O_5NCl_2$ requires C, 40·8; H, 3·1; N, 4·8%). Hydrolysis gave the 5-nitro-acid, m. p. and mixed m. p. 159—160°.

Nitration of 2 : 4-*Dichloro*-5-*nitrophenoxyacetic Acid.*—The 5-nitro-acid (2·0 g.) in concentrated sulphuric acid (10 ml.) was treated with concentrated nitric acid (2 ml.) at 30°. Isolation, as above, gave 2 : 4-dichloro-5 : 6-dinitrophenoxyacetic acid as pale yellow prisms (1·29 g.), m. p. and mixed m. p. 185° (from ethanol).

2 : 4-*Dichloro*-6-*nitrophenoxyacetic Acid.*—2 : 4-Dichloro-6-nitrophenol (52 g., 0·25 mole) in absolute alcohol (500 ml.), on addition of sodium ethoxide solution (5·75 g. of sodium in 500 ml. of alcohol) yielded the bright red salt. This mixture, after 6 hours' refluxing with *n*-butyl chloroacetate (38·8 g., 0·25 mole), contained no chloride ion. Diethylene glycol (200 ml.) was then added and the ethanol removed by slow distillation (to 150°), the red salt gradually dissolv-

ing and sodium chloride being precipitated. The crude butyl ester separated as a yellow oil when the mixture was poured into water. Ether-extraction and removal of unchanged phenol with sodium carbonate solution gave n-*butyl* 2 : 4-*dichloro*-6-*nitrophenoxyacetate* (40 g.) as a yellow viscous oil, b. p. 182—184°/2·0 mm. (Found : C, 44·8; H, 3·9. $C_{12}H_{13}O_5NCl_2$ requires C, 44·7; H, 4·1%). Hydrolysis gave the *acid*, pale yellow needles, m. p. 128—128·5° (from benzene) (Found : C, 35·9; H, 1·9; N, 5·1. $C_8H_5O_5NCl_2$ requires C, 36·1; H, 1·9; N, 5·3%).

6 : 8-*Dichloro*-3 : 4-*dihydro*-3-*oxobenzoxazine* (I; R = R′ = H; Ring Index numbering).—2 : 4-Dichloro-6-nitrophenoxyacetic acid (5·3 g.) in boiling water, (500 ml.) was treated with ferrous sulphate solution (98 g. of the heptahydrate in 500 ml. of water), and sodium hydroxide solution (28 g. in 100 ml. of water) slowly added according to Jacobs and Heidelberger's general procedure (*loc. cit.*). The *oxazine* was isolated as colourless needles (4·0 g.), m. p. 268° (from ethanol) (Found : C, 44·2; H, 2·25. $C_8H_5O_2NCl_2$ requires C, 44·1; H, 2·3%). The lactam is insoluble in 10N-hydrochloric acid but soluble in 2N-sodium hydroxide, being reprecipitated on acidification.

Catalytic Reduction of n-*Butyl* 2 : 4-*Dichloro*-6-*nitrophenoxyacetate*.—(*a*) The butyl ester (3·2 g.) in 95% ethanol (100 ml.) was shaken at room temperature and pressure with Raney nickel (pH of solution 7·5—8·0) until no further hydrogen was taken up (85% absorption). From the solution, which gave no colour with alcoholic ferric chloride solution, the insoluble lactam (I; R = R′ = H) was soon precipitated as colourless needles (1·8 g.), m. p. 268—270° (from ethanol). Butanol was detected in the filtrate.

(*b*) In an analogous reduction of the butyl ester (3·2 g.), with 10% palladium–" Norit " only 70% of the theoretical volume of hydrogen was absorbed. After removal of catalyst and solvent, 6 : 8-*dichloro*-3 : 4-*dihydro*-4-*hydroxy*-3-*oxobenzoxazine* (I; R = OH, R′ = H) crystallised as colourless needles (2·4 g.), m. p. 229—230° (from ethanol) (Found : C, 41·1; H, 2·1; N, 5·8. $C_8H_5O_3NCl_2$ requires C, 41·0; H, 2·15; N, 6·0%). It gives an intense wine-red colour with alcoholic ferric chloride, and is reduced quantitatively to the lactam (I; R = R′ = H), m. p. and mixed m. p. 269—270°, by zinc and hydrochloric acid.

5-*Amino*-6 : 8-*dichloro*-3 : 4-*dihydro*-3-*oxobenzoxazine* (I; R = H, R′ = NH_2).—2 : 4-Dichloro-5 : 6-dinitrophenoxyacetic acid (25 mg.), on reduction with zinc dust in warm 5N-hydrochloric acid solution, gave an immediate precipitate of the 5-*amino-lactam*, isolated as colourless needles (17·5 mg.), m. p. 325° (decomp.) (from ethanol) (Found : C, 41·2; H, 2·55; N, 11·9. $C_8H_6O_2N_2Cl_2$ requires C, 41·2; H, 2·6; N, 12·0%). Acetylation (sodium acetate–acetic anhydride) gave a *diacetyl* derivative which crystallised as almost colourless plates, m. p. 227—228°, from ethanol (Found : C, 45·6; H, 3·0; N, 8·8. $C_{12}H_{10}O_6N_2Cl_2$ requires C, 45·5; H, 3·15; N, 8·8%).

2 : 4-*Dichloro*-6-*hydroxyphenoxyacetic Acid*.—The 3 : 5-dichlorocatechol (Dakin, *Amer. Chem. J.*, 1909, **42**, 477) (8·0 g.; m. p. 85—86°) was added to a solution of sodium (1·15 g.) in butanol (60 ml.) under an atmosphere of hydrogen. Sodium chloride was precipitated from the pale yellow solution on addition of *n*-butyl chloroacetate (8·0 g.) during 2 hr. Direct alkaline hydrolysis of the reaction mixture, followed by steam-distillation to remove butanol, gave colourless crystals after acidification. Unchanged dichlorocatechol (1·5 g.) was recovered by repeated extraction of a sodium hydrogen carbonate solution of these phenoxyacetic acids with ether until the ethereal extracts no longer gave a positive ferric chloride test. The mixed acids (9·0 g.), obtained from the sodium hydrogen carbonate solution, were separated by repeated crystallisation from water. 2 : 4-*Dichloro*-6-*hydroxyphenoxyacetic acid* was isolated as colourless needles (3·1 g.), m. p. 132° (Found : C, 40·45; H, 2·5. $C_8H_6O_4Cl_2$ requires C, 40·5; H, 2·55%). The *methyl ester*, prepared in the normal manner, crystallised as colourless needles, m. p. 91°, from light petroleum (Found : C, 42·9; H, 3·15. $C_9H_8O_4Cl_2$ requires C, 43·1; H, 3·2%). Evaporation of the aqueous filtrate from the 6-hydroxy-acid gave 3 : 5-*dichloro*-1 : 2-*di*(*ethoxycarbonylmethoxy*)*benzene* (1·1 g.) which finally crystallised as rosettes of colourless needles, m. p. 189—191°, from benzene (Found : C, 40·6; H, 2·65. $C_{10}H_8O_6Cl_2$ requires C, 40·7; H, 2·7%).

2 : 4-*Dichloro*-6-*methoxyphenoxyacetic Acid*.—The 6-hydroxy-acid (20 mg.) was treated with an excess of methyl sulphate in 2N-sodium hydroxide, and the colourless oil formed immediately hydrolysed, to yield the 2 : 4-*dichloro*-6-*methoxyphenoxyacetic acid*, crystallising as colourless needles (20 mg.), m. p. 176°, from benzene (Found : C, 43·1; H, 3·2. $C_9H_8O_4Cl_2$ requires C, 43·1; H, 3·2%).

Cyclisation of 2 : 4-*Dichloro*-6-*hydroxyphenoxyacetic Acid*.—The 6-hydroxy-acid (50 mg.) was refluxed for 2 hr. with acetic anhydride (2 ml.). Excess of anhydride was removed under reduced pressure, to give the 5 : 7-*dichloro*-2-*oxobenzo*-1 : 4-*dioxan* (II) (40 mg.), isolated as

colourless prisms, m. p. 134—134·5°, from benzene–light petroleum (Found: C, 44·0; H, 1·95. $C_8H_4O_3Cl_2$ requires C, 43·9; H, 1·85%). This compound is insoluble in sodium hydrogen carbonate solution, but easily dissolves in warm 2N-sodium hydroxide.

Dr. E. Challen is thanked for micro-analyses.

School of Applied Chemistry, N.S.W. University of Technology,
Sydney, Australia. [*Received, October 15th*, 1953.]

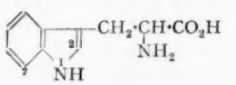
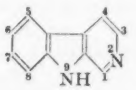
Some Methyl Derivatives of β-Carboline.

By J. W. Cook, R. M. Gailey, and J. D. Loudon.

[Reprint Order No. 4752.]

8-Methyl-, 8 : 9-dimethyl-, 1 : 8-dimethyl-, and 1 : 8 : 9-trimethyl-β-carboline and 1 : 7-dimethyltryptophan are synthesised.

7-Methyltryptophan (I) (Rydon, *J.*, 1948, 705) was converted by established methods into 8-methyl-, 8 : 9-dimethyl-, 1 : 8-dimethyl- and 1 : 8 : 9-trimethyl-β-carbolines (see II). The second and fourth of these products were also obtained from 1 : 7-dimethyltryptophan which was itself synthesised from 1 : 7-dimethyloxindole *via* the corresponding indole and gramine.

(I)  (II) 

Comparisons of recorded properties show that the base, $C_{12}H_{10}N_2$ (m. p. 176—183°), obtained from calycanthine (Barger, Madinaveitia, and Streuli, *J.*, 1939, 510) is not identical with 8-methyl-β-carboline and that "Base F," $C_{13}H_{12}N_2$ (m. p. 78—81°), obtained from alstonine (Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556) is not identical with either 8 : 9- or 1 : 8-dimethyl-β-carboline.

Experimental

N-Methylchloroacet-o-toluidide.—Benzenesulphon-*o*-toluidide was methylated in an excess of aqueous sodium hydroxide by methyl sulphate. The resultant *N-methylbenzenesulphon-o-toluidide*, m. p. 78° (from ethanol) (Found: C, 64·3; H, 5·7. $C_{14}H_{15}O_2NS$ requires C, 64·4; H, 5·8%), was hydrolysed when heated (45 min.) with a mixture of water and sulphuric acid (1 : 2, v/v). *N*-Methyl-*o*-toluidine (yield 40% from *o*-toluidine) was recovered in steam from the basified solution. Chloroacetyl chloride (3·3 g.) was slowly added to a solution of the base (3·6 g.) in benzene (25 c.c.) and pyridine (2·4 g.), and after 2 hr. *N-methylchloroacet-o-toluidide*, m. p. 46° [from light petroleum (b. p. 60—80°)], was recovered from the acid-washed benzene solution (yield, 85%) (Found: C, 60·6; H, 6·2. $C_{10}H_{12}ONCl$ requires C, 60·8; H, 6·1%).

1 : 7-*Dimethylindole*.—A mixture of *N*-methylchloroacet-*o*-toluidide (7·5 g.), aluminium chloride (7·5 g.), and sodium chloride (1·5 g.) was heated at 180—185° for 1 hr. and the cooled, powdered product was added to ice and extracted with benzene. After purification on alumina 1 : 7-*dimethyloxindole* was recovered and had m. p. 119—120° [from light petroleum (b. p. 60—80°)] (Found: C, 74·7; H, 6·9; N, 8·9. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). To a stirred suspension of this oxindole (3·5 g.) in anhydrous ether (35 c.c.) lithium aluminium hydride (1·2 g.) was slowly added. After further stirring (10 min.), water (10 c.c.) and then hydrochloric acid (10 c.c., 4%) were added and the ethereal layer was washed with acid (1 : 7-dimethylindoline was recoverable in steam from the basified acid solutions), dried, and evaporated. A solution of the residue in light petroleum (b. p. 60—80°) was passed through an alumina column, and elution with the same solvent gave 1 : 7-*dimethylindole* as needles (1·5 g.), m. p. 78° [from light petroleum (b. p. 40—60°)] (Found: C, 82·5; H, 7·7; N, 9·6. $C_{10}H_{11}N$ requires C, 82·7; H, 7·6; N, 9·7%), whereas subsequent elution with benzene afforded unchanged 1 : 7-dimethyloxindole (1 g.).

1 : 7-*Dimethyl*-3-*dimethylaminomethylindole* (1 : 7-*Dimethylgramine*).—To an aqueous solution of dimethylamine (3 c.c.; 33%), maintained below 5°, acetic acid (3 c.c.) and then formaldehyde (1·5 c.c.; 40%) were added and the whole was poured upon 1 : 7-dimethylindole (2·9 g.) which dissolved when the mixture was shaken at room temperature. After 16 hr. the solution was

basified and extracted with ether. Since the base did not readily crystallise, a portion of the ethereal solution was treated with a solution of picric acid in ether, affording 1 : 7-*dimethylgramine picrate* as orange needles, m. p. 142° (from ethanol) (Found : C, 53·0; H, 5·0; N, 16·4. $C_{13}H_{18}N_2,C_6H_3O_7N_3$ requires C, 52·9; H, 4·9; N, 16·2%). To the rest of the ethereal solution methyl iodide was added and the precipitated salt was dried *in vacuo* for use in the following experiment.

α-*Amino*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionic Acid* (1 : 7-*Dimethyltryptophan*).—A solution of the foregoing salt (0·86 g.) and ethyl acetamidomalonate (0·54 g.) in anhydrous ethanol (10 c.c.) containing sodium ethoxide (from 0·056 g. of sodium) was heated under reflux for 26 hr. Addition to water (200 c.c.) afforded *ethyl* α-*acetamido*-α-*ethoxycarbonyl*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionate*, m. p. 162° (after softening at 158°) (from ethyl acetate) (Found : C, 64·5; H, 7·2. $C_{20}H_{26}O_5N_2$ requires C, 64·2; H, 7·0%). It (3·5 g.) was heated under reflux for 18 hr. with a solution of sodium carbonate (3·5 g.) in water (35 c.c.) and, after some oil was removed in ether, the acidified solution afforded α-*acetamido*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionic acid*, m. p. 181° (from ethyl acetate) (Found : C, 65·4; H, 6·7. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6%). The acetamido-compound (1 g.) and water (50 c.c.) were heated at 200° for 6 hr. The solid obtained was extracted with dilute sulphuric acid from which 1 : 7-*dimethyltryptophan* was precipitated at pH 7 by dilute sodium hydroxide and formed colourless needles, m. p. 218°, from water (Found : C, 66·9; H, 7·1. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·95%).

8-*Methyl*-β-*carboline*.—Formaldehyde (1 c.c.; 40%) was added to a solution of 7-methyltryptophan (0·1 g.) in water (15 c.c.) and after 3 hr. at ordinary temperature the whole was heated (2 hr.) at 100° until the ninhydrin test was negative. Aqueous potassium dichromate (5 c.c.; 10%) and acetic acid (1 c.c.) were added and the solution was boiled for 3 min. Residual dichromate was reduced by addition of sodium sulphite, and the carboline was precipitated by aqueous sodium carbonate and recovered in ether. After sublimation at 150°/1 mm., 8-*methyl*-β-*carboline* formed needles, m. p. 229—230°, from benzene (Found : C, 78·9; H, 5·5; N, 15·4. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). Light absorption in ethanol : $\lambda_{max.}$ 3500, 3360, 2880, 2380 Å; log ε 3·69, 3·69, 4·17, 4·58.

1 : 8-*Dimethyl*-β-*carboline*, needles, m. p. 213° (from benzene), was obtained by using acetaldehyde (0·3 c.c.) in place of formaldehyde as in the preceding experiment (Found : C, 79·3; H, 6·4; N, 14·4. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2; N, 14·3%). Light absorption in ethanol : $\lambda_{max.}$ 3520, 3400, 2900, 2370 Å; log ε 3·63, 3·64, 4·19, 4·57.

8 : 9-*Dimethyl*-β-*carboline*.—(*a*) The condensate of 1 : 7-dimethyltryptophan and formaldehyde was prepared and oxidised as described for 8-methyl-β-carboline. 8 : 9-*Dimethyl*-β-*carboline*, after sublimation and crystallisation from methanol, melted at 68—70°, then solidified and re-melted at 96° (Found : C, 72·8; H, 6·7. $C_{13}H_{12}N_2,H_2O$ requires C, 73·1; H, 6·5%).

(*b*) A suspension of 8-methyl-β-carboline in benzene was heated under reflux with methyl sulphate for 1 hr. and, after 16 hr. at room temperature, 2 : 8-*dimethyl*-β-*carbolinium methosulphate* was collected. It formed yellow needles, m. p. 228°, from methanol (Found : C, 54·4; H, 5·2. $C_{14}H_{16}O_4N_2S$ requires C, 54·5; H, 5·2%) and when treated in aqueous solution with sodium hydroxide afforded hydrated 2 : 8-*dimethyl*-β-*carbolinium hydroxide* as yellow needles (from water), m. p. 165° re-solidifying and decomposing above 230° (Found : C, 60·35; H, 7·5. $C_{13}H_{14}ON_2,3H_2O$ requires C, 60·0; H, 7·7%). The hydroxide was heated at 100°/15 mm. for 1 hr., then suspended in dry benzene and heated with methyl iodide at 45° for 3 hr. After 12 hr. at room temperature removal of the solvent gave 2 : 8 : 9-*trimethyl*-β-*carbolinium iodide* as needles, decomp. above 320° (from water) (Found : C, 49·8; H, 4·3. $C_{14}H_{15}N_2I$ requires C, 49·7; H, 4·5%). The sublimate obtained when this iodide was heated at 300°/15 mm. was re-sublimed, affording 8 : 9-dimethyl-β-carboline (from methanol) with the same m. p. and mixed m. p. behaviour as the sample from (*a*).

1 : 8 : 9-*Trimethyl*-β-*carboline* was obtained by the foregoing methods, *viz.*, (*a*) from 1 : 7-dimethyltryptophan and acetaldehyde, and (*b*) from 1 : 8-dimethyl-β-carboline through 1 : 2 : 8-trimethyl-β-carbolinium methosulphate (m. p. 218°) and hydroxide (hydrate, m. p. 165°, re-solidifying and decomposing above 230°) and 1 : 2 : 8 : 9-tetramethyl-β-carbolinium iodide (m. p. 310°). It formed needles, m. p. 168—169°, from benzene, after sublimation at 150°/15 mm. (Found : C, 80·1; H, 6·9. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7%).

One of us (R. M. G.) gratefully acknowledges a maintenance allowance from the Department of Scientific and Industrial Research.

THE UNIVERSITY, GLASGOW, W.2. [*Received, October 26th*, 1953.]

Some Quinoline-5 : 8-quinones.

By Vladimir Petrow and Bennett Sturgeon.

[Reprint Order No. 4742.]

The preparation of some quinoline-5 : 8-quinones is described.*

The study of quinones derived from the highly antibacterial 8-hydroxyquinoline was undertaken in order to determine the effect of this structural alteration on the biological activity of the latter compound. Quinoline-5 : 8-quinone was prepared by Fischer and Renouf (*Ber.*, 1884, **17**, 1644) by oxidation of 5-amino-8-hydroxyquinoline with chromic acid. This method with appropriate modifications was employed in the present investigation. The required quinoline *Bz*-aminophenols were obtained by converting 8(5)-hydroxyquinolines into the 5(8)-nitroso-, -nitro-, or -arylazo-derivatives, which were then reduced to the corresponding amines. A choice of reducing agents was available for this purpose. Thus 8-hydroxy-5-nitrosoquinoline had been reduced with stannous chloride (von Kostanecki, *Ber.*, 1891, **24**, 153), ammonium sulphide (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2219), phenylhydrazine (Cohn, *J. pr. Chem.*, 1911, **83**, 504), or hydrogen and Raney nickel (Albert and Magrath, *Biochem. J.*, 1947, **41**, 534). An electrolytic method had been applied to 8-hydroxy-5-nitroquinoline (Gattermann, *Ber.*, 1894, **27**, 1939), and stannous chloride had been used for its 7-iodo-derivative (Matsumura, *J. Amer. Chem. Soc.*, 1927, **49**, 815). In our hands, these methods proved only of limited value, but reductions of the hydroxy-nitroso- and -nitro-quinolines with sodium dithionite (hydrosulphite) in hot, aqueous, faintly alkaline solution was simple and rapid, giving the pure amines in yields exceeding 60%.

2- and 7-Methylquinoline-5 : 8-quinone were prepared from 8-hydroxy-2- and -7-methyl-5-nitrosoquinoline, respectively. 5-Hydroxy-6-methylquinoline, required for conversion into 6-methylquinoline-5 : 8-quinone (Christiansen and Doliver, *J. Amer. Chem. Soc.*, 1941, **63**, 1470), could not be prepared by Noelting and Trautmann's procedure (*Ber.*, 1890, **23**, 3654), diazotisation of 5-amino-6-methylquinoline giving only tars. By heating 5-amino-6-methyl-8-phenylazoquinoline with 10% aqueous-alcoholic hydrochloric acid, however, hydrolysis of the 5-amino-group was achieved (cf. Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1920, **42**, 2280) with formation of 5-hydroxy-6-methyl-8-phenylazoquinoline in 60% yield. Catalytic reduction furnished the corresponding aminophenol, which passed smoothly into 6-methylquinoline-5 : 8-quinone on oxidation. 2 : 6-Dimethylquinoline-5 : 8-quinone was similarly obtained.

The preparation of 7-iodoquinoline-5 : 8-quinone was undertaken as this compound is a potential oxidation product of the amœbicide 8-hydroxy-5 : 7-di-iodoquinoline. 8-Hydroxy-5-nitroquinoline, required as an intermediate, has been obtained by oxidising 8-hydroxy-5-nitrosoquinoline (i) with alkaline potassium ferricyanide followed by sublimation of the product (Vis, *J. pr. Chem.*, 1892, **45**, 540) and (ii) with 61% nitric acid (*d* 1·38) (von Kostanecki, *loc. cit.*). Method (i) was unsuitable for preparative work. Method (ii) gave largely 8-hydroxy-5 : 7-dinitroquinoline. By using 38% nitric acid (*d* 1·24), under controlled conditions, however, it proved possible to obtain the 5-nitro-compound in yields exceeding 85%. 8-Hydroxy-5-nitrosoquinaldine was similarly converted in 60% yield into the corresponding 5-nitro-analogue, *ca.* 20% of 8-hydroxy-5 : 7-dinitroquinaldine also being formed. Bromination and iodination in aqueous alkaline solution of these two mononitro-compounds gave the 7-halogeno-derivatives which, on reduction with sodium dithionite and oxidation, furnished 7-bromo- and 7-iodo-quinoline and quinaldine-5 : 8-quinone as comparatively unstable solids which decomposed within 3—4 weeks.

Attempts to prepare 6-iodo-quinoline- and -quinaldine-5 : 8-quinone were not successful. Preparation of 6-iodoquinoline from *p*-iodoaniline by the Skraup reaction gave quinoline

* Certain compounds described herein are recorded in a paper by Long and Schofield (*J.*, 1953, 3161) published after this paper had been submitted.

as main product together with ≮5% of 6-iodoquinoline, converted into 6-iodo-5-nitroquinoline (cf. the nitration of 6-chloroquinoline; Fourneau, Trefouel, Trefouel, and Wancolle, *Bull. Soc. chim.*, 1930, **47**, 738), but the overall yield at this stage was too low for the synthesis to be pursued. Nitration of 6-iodoquinaldine gave 6-iodo-5-nitroquinaldine, the constitution of which followed from its ready condensation with aniline. The corresponding 5-amino-6-iodo-derivative, however, failed to react with benzenediazonium chloride and the preparation was consequently abandoned.

Quinoline-5 : 8-quinone is weakly basic. Its hydrochloride is decomposed by water; the quinone does not appear to form quaternary derivatives or an *N*-oxide. An indirect approach to the latter compound was consequently examined. 8-Hydroxyquinoline was smoothly converted into the *N*-oxide by treatment with perphthalic acid. This compound, in contrast to 8-hydroxyquinoline which so readily passes into the 5 : 7-dinitro-derivative, gave only 8-hydroxy-5(?)-nitroquinoline *N*-oxide on treatment with concentrated nitric acid in acetic acid. Reduction furnished 5(?)-amino-8-hydroxyquinoline *N*-oxide which did not, however, appear to yield the required 5 : 8-quinone on oxidation. Thiols readily added to the quinone but the products could not be obtained pure.

Experimental

Quinoline-5 : 8-quinone.—A solution of 5-amino-8-hydroxyquinoline sulphate (1 g.) in 10% sulphuric acid (10 ml.) was treated with sodium dichromate in a little water. When reaction was complete the mixture was extracted 4 times with chloroform (15-min. intervals), and the combined extracts were washed with water and evaporated to small bulk. Addition of light petroleum led to separation of quinoline-5 : 8-quinone (350 mg.) in light yellow needles, m. p. 129° (decomp.) (Found : C, 67·9; H, 3·1; N, 8·6. Calc. for $C_9H_5O_2N$: C, 67·7; H, 3·1; N, 8·8%). Fischer and Renouf (*loc. cit.*) give m. p. 110—120° (decomp.).

Quinaldine-5 : 8-quinone.—8-Hydroxy-5-nitrosoquinaldine (5·8 g.) in water (100 ml.) and sodium hydroxide (6·3 g.) was treated at 70° with sodium dithionite (*ca.* 13 g.) until the brown colour had disappeared. Acetic acid was added until the solution was neutral, and the 5-amino-8-hydroxyquinaldine collected after cooling. Oxidation as above furnished *quinaldine-5 : 8-quinone* (2 g.), yellow-green prisms, m. p. 145° (decomp.) (Found : C, 69·6; H, 4·2; N, 7·9. $C_{10}H_7O_2N$ requires C, 69·4; H, 4·1; N, 8·1%), after crystallising from ethanol–light petroleum (b. p. 80—100°).

5-Amino-8-hydroxy-7-methylquinoline.—The corresponding nitroso-compound (2 g.) was reduced in 10% sodium hydroxide solution with sodium dithionite (4·2 g.), the *amine* separating on cooling. It recrystallised from benzene as yellow prisms, m. p. 155° (decomp.) (Found : C, 69·0; H, 5·8; N, 16·1. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8; N, 16·2%).

7-Methylquinoline-5 : 8-quinone, obtained (55%) by oxidation of the foregoing amine, separated from ethanol–light petroleum (b. p. 80—100°) in light yellow needles, m. p. 181—182° (decomp.) (Found : C, 69·3; H, 4·1; N, 8·1. $C_{10}H_7O_2N$ requires C, 69·4; H, 4·1; N, 8·1%).

5-Amino-6-methyl-8-phenylazoquinoline Hydrochloride.—A solution of benzenediazonium chloride [from aniline hydrochloride (7 g.) and sodium nitrite (4 g.)] was added during 20 min. at 0—3° to 5-amino-6-methylquinoline (8·5 g.) in acetic acid (50 ml.) and water (200 ml.) containing sodium acetate (25 g.). The solution rapidly became dark red, after which the dye began to separate. Next morning, the *product* (9 g.) was collected and purified from ethanol–light petroleum, from which it separated in red-brown plates, m. p. 216° (Found : N, 18·9. $C_{16}H_{14}N_4$,HCl requires N, 18·8%).

5-Hydroxy-6-methyl-8-phenylazoquinoline hydrochloride, m. p. 212° (Found : N, 12·1; Cl, 9·9. $C_{16}H_{13}ON_3$,HCl,C_2H_5·OH requires N, 12·2; Cl, 9·9%), after crystallisation from ethanol, separated (7 g.) when the corresponding 5-amino-compound (12 g.) was hydrolysed by boiling it with concentrated hydrochloric acid (60 ml.), water (50 ml.), and ethanol (150 ml.) for 2½ hr., and the mixture cooled. The *base* crystallised from ethanol in fine red needles, m. p. 177° (Found : C, 73·4; H, 4·9. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·9%), after liberation with aqueous ammonia.

8-Amino-5-hydroxy-6-methylquinoline.—5-Hydroxy-6-methyl-8-phenylazoquinoline (1·5 g.) was reduced with hydrogen in ethanol in the presence of palladium–charcoal until the solution was colourless. The catalyst was removed, and the filtrate evaporated to crystallisation.

8-Amino-5-hydroxy-6-methylquinoline (500 mg.) separated from ethanol in pale brown plates, m. p. 216° (Found : C, 68·6; H, 5·8; N, 16·1. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·6; N, 16·1%).

6-Methylquinoline-5 : 8-quinone, yellow needles, m. p. 188° (decomp.) (Found : C, 69·8; H, 4·3; N, 7·9. Calc. for $C_{10}H_7O_2N$: C, 69·4; H, 4·1; N, 8·1%), after purification from chloroform–light petroleum (b. p. 60—80°), was obtained by oxidation of the foregoing compound. Christiansen and Doliver (*loc. cit.*) record m. p. 167—168°.

2 : 6-Dimethyl-5-nitroquinoline.—2 : 6-Dimethylquinoline (3·0 g.) in cold concentrated sulphuric acid (8·5 ml.) was treated with concentrated nitric acid (1·5 ml.) in concentrated sulphuric acid (2·0 ml.). After 2 hr. on the steam-bath the mixture was poured into cold dilute ammonia, and the precipitated solids were collected and purified from light petroleum. *2 : 6-Dimethyl-5-nitroquinoline* (3·8 g.) formed pale yellow prisms, m. p. 106° (Found : C, 65·5; H, 4·9; N, 13·6. $C_{11}H_{10}O_2N_2$ requires C, 65·4; H, 4·9; N, 13·9%).

5-Amino-2 : 6-dimethylquinoline, prepared by reducing the foregoing compound (2·5 g.) in 80% ethanol (25 ml.) and concentrated hydrochloric acid (1 ml.) with reduced iron (6 g.) for 1½ hr., separated (2·0 g.) from benzene–light petroleum (b. p. 80—100°) in green needles, m. p. 190° (Found : C, 77·0; H, 6·8; N, 15·8. $C_{11}H_{12}N_2$ requires C, 76·8; H, 6·9; N, 16·3%).

2 : 6-Dimethylquinoline-5 : 8-quinone separated (60%) from chloroform–light petroleum (b. p. 60—80°) in yellow plates, m. p. 150° (Found : C, 70·2; H, 4·6; N, 7·5. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8; N, 8·0%). It was obtained from the foregoing compound *via 5-amino-2 : 6-dimethyl-8-phenylazoquinoline hydrochloride* (80%), red plates with a green reflex, m. p. 210° (Found : N, 17·8. $C_{17}H_{16}N_4$.HCl requires N, 17·7%), and *5-hydroxy-2 : 6-dimethyl-8-phenylazoquinoline* (63%), dark red fluffy needles, m. p. 168° (Found : C, 73·7; H, 5·6; N, 15·3. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%), after crystallisation from ethanol. 8-Amino-5-hydroxy-2 : 6-dimethylquinoline proved very sensitive to aerial oxidation and was used directly without purification.

8-Hydroxy-5-nitroquinoline.—Finely powdered 8-hydroxy-5-nitroquinoline (3 g.) was added with vigorous stirring to a mixture of concentrated nitric acid (9 ml.) and water (6 ml.) at 17°. Oxides of nitrogen were evolved, and the nitrosoquinoline was rapidly converted into insoluble 8-hydroxy-5-nitroquinoline nitrate. After 1½ hr. with occasional stirring the mixture was diluted with water, cooled to 0°, and made alkaline with cold potassium hydroxide solution. The red potassium salt was decomposed with acetic acid, and the product collected, washed with water, and recrystallised from ethanol. 8-Hydroxy-5-nitroquinoline (2·9 g., 87%) separated in yellow needles, m. p. 180°. von Kostanecki (*loc. cit.*) gives m. p. 173° and Vis (*loc. cit.*) gives m. p. 178°.

8-Hydroxy-5-nitroquinaldine.—Finely powdered 8-hydroxy-5-nitrosoquinaldine (2 g.) was oxidised by addition to concentrated nitric acid (6 ml.) and water (4 ml.) at room temperature with stirring. As soon as the material had dissolved, the solution was diluted with water to prevent further dinitration and the precipitated nitrates were collected and decomposed as above. The mixture of bases was extracted with benzene, the soluble fraction yielding *8-hydroxy-5-nitroquinaldine*, silky yellow needles (1·3 g., 60%), m. p. 136° (Found : C, 58·6; H, 4·1; N, 13·8. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9; N, 13·7%) after crystallisation from benzene–light petroleum (b. p. 80—100°). In contact with solvent or on warming, the material changed to dark red prismatic needles.

Extraction of the benzene-insoluble fraction with pyridine gave *8-hydroxy-5 : 7-dinitroquinaldine* in small yellow needles, m. p. >300° (Found : N, 16·9. $C_{10}H_7O_5N_3$ requires N, 16·9%).

7-Halogeno-8-hydroxy-5-nitroquinolines.—The compounds listed below were prepared by the following method : The finely powdered nitro-compound (1 g.) was dissolved in water (300 ml.) containing potassium hydroxide (900 mg.) by stirring at room temperature, after which bromine or iodine (1 mol.) dissolved in a solution of the appropriate potassium salt was added. Stirring was continued at room temperature for 2 hr., and the product was then precipitated by acidification, collected, washed with ethanol, and recrystallised from 2-ethoxyethanol. Yields were 60—70%.

7-Bromo-8-hydroxy-5-nitroquinoline, felted red needles, m. p. 200° (Found : C, 39·9; H, 1·8; N, 10·3; Br, 29·6. $C_9H_5O_3N_2Br$ requires C, 40·1; H, 1·9; N, 10·4; Br, 29·7%). *7-Bromo-8-hydroxy-5-nitroquinaldine*, red plates, m. p. 265° (decomp.) (Found : C, 42·5; H, 2·3; N, 9·7; Br, 28·4. $C_{10}H_7O_3N_2Br$ requires C, 42·4; H, 2·5; N, 9·9; Br, 28·3%). *8-Hydroxy-7-iodo-5-nitroquinaldine*, bright red plates, m. p. 244° (Found : N, 8·4; I, 38·2. $C_{10}H_7O_3N_2I$ requires N, 8·5; I, 38·5%).

5-Amino-7-halogeno-8-hydroxyquinolines.—Typical reduction : Finely powdered 7-bromo-

8-hydroxy-5-nitroquinoline (1·5 g.) was added to a solution of potassium hydroxide (2·5 g.) in water (20 ml.) with vigorous stirring so as to produce as fine a suspension of the potassium salt as possible. The mixture was heated nearly to boiling, and sodium dithionite (5 g.) added. Reduction was completed by boiling for 1 min., and the solution was cooled and neutralised with acetic acid. *5-Amino-7-bromo-8-hydroxyquinoline* (900 mg., 68%) separated. It crystallised from ethyl acetate–light petroleum as light brown needles, m. p. 184° (decomp.) (Found : N, 11·4; Br, 32·7. $C_9H_7ON_2Br$ requires N, 11·7; Br, 33·4%).

5-Amino-7-bromo-8-hydroxyquinaldine formed golden-brown needles, m. p. 176° (decomp.) (Found : N, 10·7; Br, 31·5. $C_{10}H_9ON_2Br$ requires N, 11·1; Br, 31·6%). *5-Amino-8-hydroxy-7-iodoquinaldine* separated from ether–light petroleum in yellow needles, m. p. 162° (decomp.) (Found : C, 40·2; H, 3·1; N, 9·4; I, 42·2. $C_{10}H_9ON_2I$ requires C, 40·0; H, 3·0; N, 9·3. I, 42·3%).

7-Halogenoquinoline-5 : 8-quinones.—The amines were oxidised with sodium dichromate (see p. 571). The quinones were sparingly soluble in water and separated at once from the oxidation mixture. *7-Bromoquinoline-5 : 8-quinone* formed pale yellow needles, m. p. 182° (Found : N, 5·5; Br, 33·0. $C_9H_4O_2NBr$ requires N, 5·9; Br, 33·6%), after crystallisation from chloroform–light petroleum (b. p. 60—80°). *7-Iodoquinoline-5 : 8-quinone* separated from chloroform–light petroleum in unstable yellow-brown needles, m. p. 160° (decomp.) (Found : N, 4·6; I, 41·1. $C_{10}H_6O_2NI$ requires N, 4·7; I, 42·5%).

7-Bromoquinaldine-5 : 8-quinone crystallised from chloroform–light petroleum in orange-yellow needles, m. p. 178° (decomp.) (Found : N, 5·5; Br, 31·8. $C_{10}H_7O_2NBr$ requires N, 5·5; Br, 31·6%).

7-Iodoquinaldine-5 : 8-quinone formed yellow-brown needles, m. p. 160° (decomp.) (Found : N, 4·6. $C_{10}H_6O_2NI$ requires N, 4·7%).

6-Iodoquinoline.—*p*-Iodoaniline (42 g.), dry glycerol (70 g.), and arsenic pentoxide (33 g.) were heated together at 120° with mechanical stirring, and concentrated sulphuric acid (20 ml.) added dropwise at such a rate that the temperature did not rise unduly. The mixture was heated under reflux for 4 hr., diluted with water (600 ml.), filtered (charcoal), and basified with ammonia solution The crude product was extracted with benzene, which was then in turn extracted with 6N-hydrochloric acid. The bases were liberated with sodium hydroxide, isolated with chloroform, and distilled at 1 mm. After a forerun of quinoline, identified as the picrate, m. p. 203°, 6-iodoquinoline passed over at 120° and was recrystallised from light petroleum, forming pale yellow prisms, m. p. 88°. Ullmann (*Annalen*, 1904, **332**, 80) gives m. p. 91°.

6-Iodo-5-nitroquinoline.—The foregoing base (1·5 g.) in concentrated sulphuric acid (4·5 ml.) was treated with concentrated nitric acid (0·8 ml.) in concentrated sulphuric acid (1·0 ml.), and the mixture heated at 100° for 1 hr. *6-Iodo-5-nitroquinoline* was precipitated when the mixture was poured into aqueous ammonia, and after recrystallisation from light petroleum (b. p. 80—100°) containing a drop of benzene formed pale yellow needles (1·5 g.), m. p. 163° (Found : N, 9·1. $C_9H_5O_2N_2I$ requires N, 9·3%).

6-Iodoquinaldine.—*p*-Iodoaniline (25 g.) was mixed with concentrated hydrochloric acid (20 ml.) and paraldehyde (20 ml.) under an efficient reflux condenser. After being kept overnight the mixture was refluxed for 2 hr., water added, and the solution decanted from the resinous residue, which was extracted twice with 2N-hydrochloric acid. The combined acid extracts (charcoal) were basified to give 6-iodoquinaldine (5·9 g.), prisms, m. p. 112° (Found : N, 5·1. Calc. for $C_{10}H_8NI$: N, 5·2%), after crystallisation from light petroleum (b. p. 60—80°). Borscher, Weissmann, and Fritzsche (*Ber.*, 1924, **57**, 1772) give m. p. 107—108°.

6-Iodo-5-nitroquinaldine separated from ethanol in pale yellow needles (90%), m. p. 146° (Found : N, 9·1; I, 41·3. $C_{10}H_7O_2N_2I$ requires N, 8·9; I, 40·5%).

6-Anilino-5-nitroquinaldine.—6-Iodo-5-nitroquinaldine (5·0 g.) was heated with aniline (25 g.) at 180° for 2 hr. Sodium acetate solution was added, and excess of aniline removed in steam. The residue was extracted with benzene, and the dried extract percolated through a column of alumina (10 cm. × 7 sq. cm.) and evaporated. Crystallisation of the residue from ethanol yielded *6-anilino-5-nitroquinaldine*, felted orange needles, m. p. 147—148° (Found : N, 14·9. $C_{16}H_{13}O_2N_3$ requires N, 15·1%).

5-Amino-6-iodoquinaldine.—The nitro-compound (2·5 g.), reduced iron (7·0 g.), and ethanol (20 ml.) containing 5 drops of concentrated hydrochloric acid were heated under reflux for 2 hr. The solids were removed by filtration and extracted twice with ethanol, and the combined extracts basified with aqueous ammonia and evaporated. *5-Amino-6-iodoquinaldine* (2 g.) separated from benzene–light petroleum (b. p. 80—100°) in golden plates, m. p. 206° (decomp.) (Found : N, 10·0; I, 44·8. $C_{10}H_9N_2I$ requires N, 9·9; I, 44·7%).

8-*Hydroxyquinoline* N-*Oxide*.—8-Hydroxyquinoline (2 g.) in chloroform was mixed with ethereal perphthalic acid (2 mols.). The following day the mixture was taken to dryness, and the residue ground with aqueous ammonia and purified from benzene–light petroleum. 8-*Hydroxyquinoline* N-*oxide* formed golden-yellow needles, m. p. 138° (Found: C, 67·5; H, 4·2; N, 8·6. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%).

8-*Hydroxy*-5(?)-*iodoquinoline* N-*Oxide*.—Iodine (5·1 g.) in aqueous potassium iodide solution was added dropwise to a solution of the foregoing base (3·2 g.) in 0·2% sodium hydroxide solution (400 ml.). The *oxide* was collected after 24 hr., dried, and extracted with benzene, forming yellow needles, m. p. 169° (Found: N, 4·9; I, 44·3. $C_9H_6O_2NI$ requires N, 4·9; I, 43·7%).

8-*Hydroxy*-5(?)-*nitroquinoline* N-*Oxide*.—A solution of 8-hydroxyquinoline *N*-oxide (1·6 g.) in acetic acid (10 ml.) was treated at $>20°$ with concentrated nitric acid (1 ml.). After 1 hr. the nitrate was collected and decomposed by reprecipitation from 5N-potassium hydroxide with acetic acid. The *nitro*-derivative (70%) separated from ethanol in small yellow needles, m. p. 191—193° (Found: C, 52·4; H, 3·1; N, 13·4. $C_9H_6O_4N_2$ requires C, 52·4; H, 2·9; N, 13·5%).

8-*Hydroxy*-5(?)-*nitrosoquinoline* N-*Oxide*.—8-Hydroxyquinoline *N*-oxide (1·6 g.) was dissolved in concentrated hydrochloric acid (5·0 ml.) and cooled to 0°, the hydrochloride crystallising. Sodium nitrite (900 mg.) in a little water was added; the hydrochloride rapidly dissolved and an orange product separated. This was collected after 45 min., dissolved in the minimum of 5N-potassium hydroxide, and reprecipitated with dilute acetic acid. 8-*Hydroxy*-5(?)-*nitrosoquinoline* N-*oxide* was purified by extraction with alcohol and formed a light brown powder, m. p. 217—218° (decomp.) (Found: C, 56·8; H, 3·7; N, 14·5. $C_9H_6O_3N_2$ requires C, 56·8; H, 3·2; N, 14·8%).

5(?)-*Amino*-8-*hydroxyquinoline* N-*Oxide*.—The foregoing compound (2·0 g.) was dissolved in hot water containing potassium hydroxide (3·4 g.) and sodium dithionite (5·5 g.) was added. The *amine* separated on cooling and was purified from benzene to give orange-red needles, m. p. 180—182° (decomp.) (Found: C, 61·3; H, 4·5; N, 16·0. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·5; N, 15·9%).

6(7)-*Anilinoquinoline*-5 : 8-*quinone*.—Quinoline-5 : 8-quinone (750 mg.) and redistilled aniline (1·2 g.) were heated under reflux in ethanol (10 ml.) for 1 hr., and the deep red solution was poured into dilute acetic acid. The precipitated solids were purified from benzene–light petroleum (b. p. 80—100°), to give the quinone in scarlet needles, m. p. 213° (decomp.) (Found: C, 72·0; H, 4·2; N, 11·3. Calc. for $C_{15}H_{10}O_2N_2$: C, 72·0; H, 4·0; N, 11·2%). Fischer and Renouf (*loc. cit.*) give m. p. *ca.* 190°.

6-*Anilino*-7-*bromoquinoline*-5 : 8-*quinone*.—7-Bromoquinoline-5 : 8-quinone (100 mg.), aniline hydrochloride (53 mg.), and sodium acetate (50 mg.) were heated under reflux in alcohol (5 ml.) for 2 hr. The solution was poured into water, and the product collected and recrystallised from benzene–light petroleum (b. p. 80—100°). 6-*Anilino*-7-*bromoquinoline*-5 : 8-*quinone* (100 mg.) separated in dark red prisms, m. p. 189° (decomp.) (Found: C, 55·2; H, 2·7; N, 8·2; Br, 24·0. $C_{15}H_9O_2N_2Br$ requires C, 54·7; H, 2·7; N, 8·5; Br, 24·3%).

8-*Hydroxy*-7-*morpholinomethyl*-5-*nitroquinoline*.—8-Hydroxy-5-nitroquinoline (2 g.) in ethanol (20 ml.) under reflux was treated with formaldehyde (2 ml. of 36%) and morpholine (2 ml.). The *product* separated almost immediately. It was collected after 30 min. and purified from 2-ethoxyethanol, from which it separated in small yellow needles (2·3 g.), m. p. 231° (decomp.) (Found: C, 58·2; H, 5·4; N, 14·7. $C_{14}H_{15}O_4N_3$ requires C, 58·2; H, 5·2; N, 14·5%). Catalytic reduction in 2-ethoxyethanol, followed by oxidation, gave the *quinone*, yellow prisms which rapidly discoloured, m. p. 112° (decomp.) (Found: C, 63·6; H, 5·7; N, 11·6. $C_{14}H_{14}O_3N_2$ requires C, 65·1; H, 5·4; N, 10·8%).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., N.1.

[*Received, October 22nd,* 1953.]

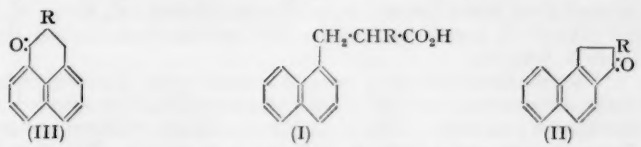
Intramolecular Acylation. Part I. The Ring Closure of Some α-Substituted β-1-Naphthylpropionic Acids.

By M. F. Ansell.

[Reprint Order No. 4743.]

The ring closure of four α-substituted β-1-naphthylpropionic acids by the action of anhydrous hydrogen fluoride has been shown to yield in each case a mixture of the corresponding 2-substituted perinaphthan-1-one and 2-substituted 4 : 5-benzindan-1-one.

The products formed when four α-substituted β-1-naphthylpropionic acids (I) were cyclised with anhydrous hydrogen fluoride have been examined chromatographically to determine whether they contained any of the corresponding 2-substituted 4 : 5-benzindan-1-one (II). For although the main product, and often the only product isolated, from such a reaction is the 2-substituted perinaphthan-1-one (III) (Johnson, "Organic Reactions," Vol. II, p. 126), Fieser and Gates (*J. Amer. Chem. Soc.*, 1940, **62**, 2335) have shown that the cyclisation of β-1-naphthylpropionic acid (I; R = H) yields both perinaphthan-1-one (III; R = H) and 4 : 5-benzindan-1-one (II; R = H). The apparent preferential formation of a 4 : 5-benzindan-1-one has been reported by Ansell and Hey (*J.*, 1950, 2874) who found that when α-1-naphthylmethylglutaric acid (I; R = $\cdot CH_2 \cdot CH_2 \cdot CO_2H$) was treated with anhydrous hydrogen fluoride the only isolatable product was β-(1-oxo-4 : 5-benzindan-2-yl)propionic acid (II; R = $CH_2 \cdot CH_2 \cdot CO_2H$).



(III) (I) (II)

The cyclisation of α-1-naphthylmethylpropionic acid (I; R = Me) with anhydrous hydrogen fluoride has been reported by Fieser and Novello (*J. Amer. Chem. Soc.*, 1940, **62**, 1855) to yield 2-methylperinaphthan-1-one (a liquid) as the sole product. It has now been shown that Fieser and Novello's product was a mixture of 2-methylperinaphthan-1-one (III; R = Me) (m. p. 50—51°) and 2-methyl-4 : 5-benzindan-1-one (II; R = Me) (m. p. 71—72°), which can be separated by chromatography. The structures of these products were established by oxidation to naphthalic and naphthalene-1 : 2-dicarboxylic acid respectively.

α-1-Naphthylmethylbutyric acid (I; R = Et), prepared by the hydrolysis and decarboxylation of ethyl ethyl-1-naphthylmethylmalonate, is a solid, m. p. 85—86°, and not a liquid as reported by Mayer and Sieglitz (*Ber.*, 1922, **55**, 1835). The cyclisation of this acid, by the action of aluminium chloride on the acid chloride, to 2-ethylperinaphthan-1-one (III; R = Et) (liquid) has been recorded by Mayer and Sieglitz (*loc. cit.*). With anhydrous hydrogen fluoride, the initial product is a liquid, which was separated by chromatography into 2-ethylperinaphthan-1-one (III; R = Et) (liquid) and 2-ethyl-4 : 5-benzindan-1-one (II; R = Et) (solid). The structures were proved as for the methyl analogues.

Cyclisation of α-1-naphthylmethylvaleric acid (I; R = Pr^n), prepared as for the butyric acid, with anhydrous hydrogen fluoride yielded a mixture of 2-*n*-propylperinaphthan-1-one (III; R = Pr^n) and 2-*n*-propyl-4 : 5-benzindan-1-one (II; R = Pr^n), which was separated by chromatography. The structure of the former was proved by oxidation to naphthalic acid. Naphthalene-1 : 2-dicarboxylic acid could not be isolated on oxidation of the latter, but its structure is considered to be certain.

When 2-1'-naphthylmethylhexanoic acid * (I; R = Bu^n), prepared as above, was cyclised with anhydrous hydrogen fluoride, a mixture of 2-*n*-butylperinaphthan-1-one

* Geneva nomenclature, CO_2H = 1.

(III; R = Bu^n) and 2-*n*-butyl-4 : 5-benzindan-1-one (II; R = Bu^n) was obtained together with a considerable amount of viscous unidentified material. In this cyclisation the yield of the 4 : 5-benzindane derivative exceeded that of the perinaphthan-1-one derivative. This appears to provide an example of the preferential formation of a five-membered ring (cf. Ansell and Hey, *loc. cit.*). It is possible however that some of the 2-*n*-butyl perinaphthan-1-one had undergone self-condensation to yield the tarry by-product.

Experimental

In all the reactions with anhydrous hydrogen fluoride "Polythene" beakers were used and the reactions carried out in the open under shelter. Light petroleum used had b. p. 60—80°.

The yellow ketones described below could not be obtained colourless by recrystallisation; they probably owe their colour to contamination by perinaphthenones (Ansell and Berman, unpublished work).

Cyclisation of α-1-Naphthylmethylpropionic Acid.—A solution of the acid (20 g.) (Fieser and Novello, *loc. cit.*) in anhydrous hydrogen fluoride (100 g.) was kept for 24 hr. at room temperature, then poured on ice and extracted with ether. After being washed with water and 5% sodium hydrogen carbonate solution and dried (Na_2SO_4), the ethereal extract was evaporated to a viscous yellow oil (17·7 g.). The latter was dissolved in light petroleum (250 c.c.) and chromatographed through alumina (44 × 4 cm.). Elution was carried out with light petroleum. The first fractions yielded *2-methylperinaphthan-1-one* (13·0 g.), m. p. 46—50°. Crystallisation from ice-cold alcohol yielded pale yellow plates, m. p. 50—51° (Found: C, 85·3; H, 5·8. $C_{14}H_{12}O$ requires C, 85·7; H, 6·1%) [oxime, m. p. 150—152°; Fieser and Novello (*loc. cit.*) record m. p. 147·2—148·2°]. The second series of fractions from the chromatography yielded *2-methyl-4 : 5-benzindan-1-one* (1·9 g.), m. p. 66—72°. Crystallisation from ice-cold alcohol gave yellow prisms, m. p. 71—72° (Found: C, 85·1; H, 6·0. $C_{14}H_{12}O$ requires C, 85·7; H, 6·1%) [*oxime*, m. p. 168—170° (needles from alcohol) (Found: N, 6·7. $C_{14}H_{13}ON$ requires N, 6·6%)].

Oxidation of 2-methylperinaphthan-1-one. A solution of 2-methylperinaphthan-1-one (1·0 g.) and sodium dichromate (7·5 g.) in glacial acetic acid (25 c.c.) was heated under reflux for 30 min. and then poured into water. The precipitated solid was collected and sublimed at 230° under reduced pressure, to give naphthalic anhydride, m. p. 272—274°, raised to 274—278° on admixture with an authentic specimen.

Oxidation of 2-methyl-4 : 5-benzindan-1-one. 2-Methyl-4 : 5-benzindan-1-one (0·8 g.), was heated at 60—70° for 24 hr. with potassium ferricyanide (50 g.) and potassium hydroxide (9·0 g.) in water (180 c.c.). When cold the solution was filtered and acidified. The precipitated acid was collected and sublimed at 180—200° under reduced pressure, to yield naphthalene-1 : 2-dicarboxylic anhydride in needles, m. p. 166—167° raised to 167—168° on admixture with an authentic specimen.

Ethyl Ethyl-1-naphthylmethylmalonate.—To a solution of sodium ethoxide prepared from anhydrous alcohol (250 c.c.) and sodium (15 g., 0·65 mole) was added ethyl ethylmalonate (131·6 g., 0·7 mole), followed by 1-naphthylmethyl chloride (Grummitt and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 295) (88·3 g., 0·5 mole). The whole was heated under reflux for 4 hr., cooled, diluted with water, and neutralised with 2N-hydrochloric acid. The organic layer was separated and the aqueous layer extracted twice with ether. The combined extracts were washed with dilute sodium carbonate solution, followed by 2N-hydrochloric acid, and dried (Na_2SO_4). Removal of the ether, followed by distillation at 15 mm. to remove unchanged ethyl ethylmalonate, left a residue which on distillation yielded ethyl ethyl-1-naphthylmethylmalonate (133 g.), b. p. 160—162°/0·02 mm. Mayer and Sieglitz (*loc. cit.*) record b. p. 227°/12 mm.

α-1-Naphthylmethylbutyric Acid.—The above ester (133 g.) in alcohol (133 c.c.) was heated under reflux for 6 hr. with potassium hydroxide (133 g.) in water (133 c.c.). After removal of the alcohol the residue was diluted with water and acidified. The solid which separated was collected and decarboxylated at 170—180° for 45 min. A solution of the resulting acid in aqueous sodium hydroxide solution was extracted with ether, and the aqueous solution was acidified and extracted with ether. Evaporation of the final dried (Na_2SO_4) ethereal solution yielded an oil which when cooled and scratched solidified. Recrystallisation from light petroleum (b. p. 60—80°) containing a trace of benzene gave *α-1-naphthylmethylbutyric acid* (83·5 g.), m. p. 79—83°. Further recrystallisation raised the m. p. to 85—86° (Mayer and Sieglitz, *loc. cit.*, reported this acid as a liquid, b. p. 223—227°/15 mm.) (Found: C, 78·9; H, 7·2. $C_{15}H_{16}O_2$ requires C, 78·95; H, 7·1%).

Cyclisation of α-1-*Naphthylmethylvaleric Acid.*—This acid (20 g.) was cyclised as in the preceding case, to yield a yellow oil (17·7 g.). The latter was chromatographed in light petroleum through alumina (44 × 4 cm.). Elution was carried out with light petroleum and finally with light petroleum–ether (9 : 1). The first fractions yielded 2-ethylperinaphthan-1-one (11·5 g.) as a viscous yellow liquid, b. p. 160—168°/1·0 mm. (Mayer and Sieglitz, *loc. cit.*, record b. p. 195°/15 mm.) (Found: C, 86·4; H, 6·9. Calc. for $C_{15}H_{14}O$: C, 85·7; H, 6·7%), which gave a *semicarbazone*, small needles (from alcohol), m. p. 212° (Found: N, 15·5. $C_{16}H_{17}ON_3$ requires N, 15·7%). The later fractions from the chromatography solidified, to yield 2-*ethyl*-4 : 5-*benzindan*-1-*one* (2·0 g.), m. p. 54—58°. Recrystallisation raised the m. p. to 64—65° (Found: C, 85·9; H, 6·6%) [*semicarbazone*, small needles (from alcohol), m. p. 232—234° (Found: N, 15·7%)].

2-Ethylperinaphthan-1-one (0·8 g.) was oxidised, as was 2-methyl-4 : 5-benzindan-1-one, to naphthalic anhydride, m. p. 272—274°, raised to 274—278° on admixture with an authentic specimen.

2-Ethyl-4 : 5-benzindan-1-one (0·8 g.) was oxidised, as was 2-methyl-4 : 5-benzindan-1-one, to naphthalene-1 : 2-dicarboxylic anhydride, m. p. 166—167°, raised to 167—168° on admixture with an authentic specimen.

Ethyl 1-*Naphthylmethyl*-(n-*propyl*)*malonate.*—This *ester* was prepared in the same way as ethyl ethyl-1-naphthylmethylmalonate (yield, 123 g.) and had b. p. 168—170°/0·6 mm. (Found: C, 74·1; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·6%).

α-1-*Naphthylmethylvaleric Acid.*—Ethyl 1-naphthylmethyl-(*n*-propyl)malonate (120 g.) was hydrolysed and decarboxylated as was ethyl ethyl-1-naphthylmethylmalonate to yield, after recrystallisation from light petroleum, α-1-*naphthylmethylvaleric acid* (66·0 g.), m. p. 84—85°. Further recrystallisation raised the m. p. to 85—86° (Found: C, 79·6; H, 7·4. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%).

Cyclisation of α-1-*Naphthylmethylvaleric Acid.*—This acid (20 g.) was cyclised as was α-methyl-β-1-naphthylpropionic acid, to yield a yellow oil (17·5 g.). Chromatography in light petroleum through alumina, and elution with light petroleum, gave, first, 2-n-*propylperinaphthan*-1-*one* (13·5 g.; m. p. 60—62°), needles, m. p. 62—63° (from ice-cold alcohol) (Found: C, 85·7; H, 7·0. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%) [*semicarbazone* (needles from alcohol), m. p. 202—204° (Found: N, 14·8. $C_{17}H_{19}ON_3$ requires N, 15·0%)], then 2-n-*propyl*-4 : 5-*benzindan*-1-*one* (2·1 g.; m. p. 32—35°), pale yellow crystals (from ice-cold alcohol), m. p. 35—36° (Found: C, 85·7; H, 7·0%) [*semicarbazone* (needles from alcohol), m. p. 218—220° (Found: N, 14·7%)].

2-*n*-Propylperinaphthan-1-one (1·0 g.) was oxidised as above to naphthalic anhydride, m. p. 272—274° raised to 274—276° on admixture with an authentic specimen.

Ethyl n-*Butyl*-1-*naphthylmethylmalonate.*—This *ester*, prepared from ethyl *n*-butylmalonate and 1-naphthylmethyl chloride as above (yield, 130 g.), had b. p. 154—156°/0·002 mm. (Found: C, 74·7; H, 7·9. $C_{22}H_{28}O_4$ requires C, 74·5; H, 7·8%). On hydrolysis it (110 g.) gave 2-1′-*naphthylmethylhexanoic acid* (61·0 g.), m. p. 64—66° (from light petroleum plus a trace of benzene) (Found: C, 79·4; H, 7·7. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%).

Cyclisation of 2-1′-*Naphthylmethylhexanoic Acid.*—This acid was cyclised as above to a reddish oil (17·8 g.). Chromatography in light petroleum (200 c.c.) through alumina (44 × 4 cm.), elution with light petroleum, and recrystallisation from ice-cold alcohol gave 2-*n*-*butylperinaphthan*-1-*one* (1·7 g.), m. p. 30—31° (Found: C, 85·8; H, 7·5. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%) [*semicarbazone* (small needles from alcohol), m. p. 196—198° (Found: C, 73·0; H, 6·9; N, 14·6. $C_{18}H_{21}ON_3$ requires C, 73·0; H, 7·0; N, 14·2%)]. Further elution with light petroleum–benzene (9 : 1) yielded a semi-solid fraction (0·3 g.), followed by 2-n-*butyl*-4 : 5-*benzindan*-1-*one* (4·0 g.), m. p. 46—48°. Recrystallisation from ice-cold alcohol yielded colourless plates, m. p. 52—53° (Found: C, 85·6; H, 7·5%); the *semicarbazone* formed needles (from alcohol), m. p. 222—223° (introduced at 200°) (Found: C, 73·2; H, 7·2; N, 14·1%). Continued elution yielded a viscous red oil (10·3 g.) which did not solidify.

2-*n*-Butylperinaphthan-1-one (1·0 g.) was oxidised as above to naphthalic anhydride, m. p. 273—275° raised to 274—276° on admixture with an authentic specimen.

The author is indebted to the Central Research Fund of London University and to the Chemical Society for financial assistance.

QUEEN MARY COLLEGE, UNIVERSITY OF LONDON,
MILE END ROAD, LONDON, E.1.

[*Received, October 22nd,* 1953.]

Studies on Bond Type in Certain Cobalt Complexes. Part V. The Exchange Reactions of Cobaltous* 1 : 10-*Phenanthroline and Tripyridyl Complexes.*

By B. O. West.

[Reprint Order No. 4680.]

The exchange of cobalt ions with [tris-(1 : 10-phenanthroline)cobalt(II)]$^{++}$, [tris-(5-methyl-1 : 10-phenanthroline)cobalt(II)]$^{++}$, and [tris-(5-nitro-1 : 10-phenanthroline)cobalt(II)]$^{++}$ is very rapid at 15° and 0·005M-concentrations. With [bistripyridylcobalt(II)]$^{++}$, however, under analogous conditions slow exchange ($t_{\frac{1}{2}}$ = 2·8 hr.) is observed.

The exchange of cobaltous ions with several cobalt–1 : 10-phenanthroline complexes and bis-αα′α″-tripyridylcobalt(II) dibromide has been investigated in aqueous solution at 15°, the results being presented in the Table. It can be seen that the exchange of phenanthroline complexes is much more rapid than that of the tripyridyl complex under comparable conditions.

The exchange of cobalt ions with cobaltous complexes of several o-*phenanthrolines and tripyridyl at* 15°.

	Concn., M		
Complex	Complex	$CoSO_4$	$t_{\frac{1}{2}}$
$[Co(1 : 10\text{-phenanthroline})_3]^{++}$	0·005	0·005	<28 sec.
$[Co(5\text{-methyl-}1 : 10\text{-phenanthroline})_3]^{++}$	,,	,,	<36 sec.
$[Co(5\text{-nitro-}1 : 10\text{-phenanthroline})_3]^{++}$	,,	,,	<25 sec.
$[Co(tripyridyl)_2]^{++}$	,,	,,	2·8 hr.

With regard to the 1 : 10-phenanthroline complexes, Brandt and Gullstrom (*J. Amer. Chem. Soc.*, 1952, **74**, 3532) have shown that the stabilities of the corresponding ferrous derivatives increase in the order $NO_2<H<CH_3$, *i.e.*, that of the dissociation constants of the free bases. On the assumption that the stabilities of the cobalt compounds would follow the same order, it had been hoped to discover differences in the ease of exchange of the cobalt *o*-phenanthroline complexes also in the same order. However, although the upper limits for the $t_{\frac{1}{2}}$ values of these compounds do lie in this order, exchange proceeded too rapidly for accurate measurements of $t_{\frac{1}{2}}$ to be made, and the order may be fortuitous.

This rapid exchange, however, leads to the conclusion that ionic or weakly covalent bonds are present in the three cobalt–phenanthroline complexes. This view is supported by magnetic evidence. Cambi and Cagnasso (*Atti R. Accad. Lincei*, 1934, **19**, 458) give the value of 5·1 B.M. for the magnetic moment of the corresponding dibromide of the unsubstituted *o*-phenanthroline complex, which implies "ionic-type" bonds in this compound. One may expect that similar moments would be found for the two substituted phenanthroline complexes.

The tris-(1 : 10-phenanthroline)ferrous compound has been shown to undergo extremely slow exchange (Ruben, Kamen, *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2297), which may be reconciled with the strong covalent bonding indicated by its diamagnetism (Biltz, *Z. anorg. Chem.*, 1928, **170**, 161).

The magnetic moment of the tripyridyl–cobalt complex has not been determined, so no direct evidence as to the bonds existing in this complex is available. One may suggest covalent $3d^24sp^3$ bonding on the basis of the slow exchange rate, bearing in mind the *o*-phenanthroline ferrous complex where slow exchange and strong covalent bonding apparently are complementary. However, in view of the pronounced stabilising effect brought about by an increase in the number of chelate rings per molecule of base (Burkin, *Quart. Reviews*, 1951, **5**, 10), this factor may be causing the increased stability of the tripyridyl over the

* Part IV, *J.*, 1954, 395.

formally analogous phenanthroline derivatives. Nevertheless, Morgan and Burstall (*J.*, 1937, 1649) have shown that the complex may be oxidised to the cobaltic state by fairly powerful oxidisers such as chlorine, which could mean that the complex did have covalent bonds of the $3d^2 4s 4p^3$ hybrid type and one 3*d* electron had been promoted to the more energetic 5*s* orbital, whence it could be more easily removed by oxidising agents.

It is significant that Pfeiffer and Werdelmann (*Z. anorg. Chem.*, 1950, **261**, 197) have observed that the tris-1 : 10-phenanthroline complex is extremely resistant to oxidation—a situation to be expected if all unpaired electrons lay in 3*d* orbitals as in the free ion. The measured moment shows that such a configuration is certainly present in this complex.

Experimental

Exchange Procedure.—Equal volumes (2 c.c.) of solutions of the complex and cobalt sulphate, the latter labelled with ^{60}Co, at appropriate concentrations were mixed in small flasks in a thermostat. After the required time interval excess of an aqueous solution of $K_2[CdI_4]$ was added, which precipitated each complex studied as the $[CdI_4]^{2-}$ salt. This was filtered off and dissolved in hot concentrated nitric acid. The resulting solution and the filtrate containing cobalt sulphate were each made up to a standard volume, and aliquot portions were counted in a liquid-type counter.

Radioactive ^{60}Co.—This was obtained from the American Atomic Energy Commission through the courtesy of C.S.I.R.O.

Phenanthroline Complexes.—These were all prepared by Pfeiffer and Werdelmann's method (*loc. cit.*) for the unsubstituted complex. The composition of tris-(1 : 10-phenanthroline)-cobalt(II) dichloride septahydrate was verified [Found : C, 54·6; H, 4·7. Calc. for $(C_{12}H_8N_2)_3CoCl_2,7H_2O$: C, 54·3; H, 4·8%].

Tris-5-methyl-1 : 10-phenanthrolinecobalt(II) *dichloride hexahydrate.* Cobalt chloride hexahydrate (0·24 g., 1 mol.) was dissolved in the minimum quantity of hot water, and the solution added to a warm suspension of 5-methyl-1 : 10-phenanthroline (0·65 g., 3 mols.) in water (10 c.c.). The base rapidly dissolved, and the solution darkened and was filtered and set aside. A light yellow powder was soon precipitated. This was filtered off and redissolved in warm water. The light yellow powder was reprecipitated as soon as the source of heat was removed, and was filtered off and dried in the air [Found : C, 56·9; H, 5·6; Co, 6·7. $(C_{13}H_{10}N_2)_3CoCl_2,6H_2O$ requires C, 57·1; H, 5·2; Co, 7·0%].

Tris-5-nitro-1 : 10-phenanthrolinecobalt(II) *dichloride nonahydrate.* Cobalt chloride hexahydrate (0·24 g., 1 mol.) in water was added to a suspension of 5-nitro-1 : 10-phenanthroline (0·75 g., 3·3 mols.) in water. When no more base would dissolve the solution was filtered and evaporated to crystallization. Yellow-brown prisms were obtained which were recrystallized from water and air-dried [Found : C, 44·7; H, 4·0; Co, 6·0. $(C_{12}H_7N_3O_2)_3CoCl_2,9H_2O$ requires C, 44·7; H, 4·01; Co, 6·1%].

Bis-αα′α″-tripyridylcobalt(II) *dibromide.* This was prepared by Morgan and Burstall's method (*loc. cit.*) as a hydrate [Found : C, 47·9; H, 4·0; N, 11·2. Calc. for $(C_{15}H_{11}N_3)_2CoBr_2,3{\cdot}5H_2O$: C, 48·1; H, 3·9; N, 11·2%].

Johnson Chemical Laboratories, University of Adelaide,
South Australia. [*Received, September 28th*, 1953.]
[Present address : University Chemical Laboratory, Cambridge.]

The Retardation of Benzaldehyde Autoxidation. Part VI. The Actions of a Number of Polycyclic Aromatic Hydrocarbons of Carcinogenic Interest.*

By J. R. Dunn, William A. Waters, and (in part) Ivan M. Roitt.

[Reprint Order No. 4700.]

Kinetic study of the retardation of the benzoyl peroxide-catalysed autoxidation of benzaldehyde by anthracene and by 1 : 2-5 : 6-dibenzanthracene indicates that chain termination is initially effected by combination of benzoylperoxy-radicals, Ph·CO·O·O·, with the hydrocarbon. After longer periods of action polycyclic hydrocarbons of different structure show differences in type of behaviour and classification into the following groups is possible: *A*, hydrocarbons which are initially inhibitory but are oxidised to products having no such action; *B*, good initial inhibitors which are oxidised to products that are also inhibitors; *C*, very poor inhibitors which are oxidised to more effective inhibitors. Carcinogenic activity seems to be associated mainly with the hydrocarbons of group *B*.

The maximum free valency numbers, $F_{max.}$, of polycyclic aromatic hydrocarbons can be correlated with their relative efficiencies as retarders of the initial stage of benzaldehyde autoxidation. Their eventual retarding efficiency can, to some extent, be correlated with the redox potentials of the corresponding quinones.

It is well known that certain polycyclic aromatic hydrocarbons can retard the autoxidation of benzaldehyde. Branch, Almquist, and Goldsworthy (*J. Amer. Chem. Soc.*, 1933, **55**, 4052) showed that anthracene was an effective initial inhibitor of this autoxidation and that the inhibiting action ceased when all the anthracene had been destroyed, presumably by oxidation to anthraquinone which Bäckström and Beatty (*J. Phys. Chem.*, 1950, **35**, 2530) had isolated in 80% yield from this same system. Benzaldehyde autoxidation was also chosen by Wasley and Rusch (*Cancer Res.*, 1942, **2**, 422) for studying both the inhibiting powers and the induced oxidations of anthracene, 1 : 2-benzanthracene, 1 : 2-5 : 6-dibenzanthracene, 20-methylcholanthrene, and 3 : 4-benzopyrene. They showed, *inter alia*, that 3 : 4-benzopyrene was thereby oxidised to a mixture of the 5 : 8- and the 5 : 10-quinone which are also autoxidation inhibitors (Muller and Rusch, *ibid.*, 1945, **5**, 480) and are toxic, though not carcinogenic (Berenblum and Schoental, *ibid.*, 1943, **3**, 145). Lisle (*ibid.*, 1951, **11**, 153), from a study of the effects of a number of compounds on the rate of decolorisation of an autoxidising solution of indigo-carmine in benzaldehyde, has placed polycylic aromatic hydrocarbons in the order: 3 : 4-benzopyrene, 20-methylcholanthrene > anthracene, pyrene (all powerful inhibitors) $\geqslant$ 1 : 2-5 : 6-dibenzanthracene (moderate) > chrysene, 2 : 3-benzophenanthrene (weak inhibitors).

Since the active carcinogenic agents can act as inhibitors of biological oxidations (cf. Boyland, *Nature*, 1932, **130**, 274: Joyet-Lavergne, *Compt. rend.*, 1944, **219**, 494), presumably by affecting certain types of enzyme oxidase systems (Rusch and Kline, *Cancer Res.*, 1941, **1**, 465), the possibility of correlating carcinogenic action with the inhibition of the chemical autoxidations of compounds of lipoid type was naturally envisaged by Rusch and his colleagues, and Lisle had aimed at devising, on this basis, a simple colour test for carcinogenic potency. Magat and Bonême (*Compt. rend.*, 1951, **232**, 1657) have found that both carcinogenic and non-carcinogenic hydrocarbons can inhibit the polymerisation of styrene and emphasise the fact that this is due to reactions of the hydrocarbons with free radicals. From the foregoing results Kooyman and Heringa (*Nature*, 1952, **170**, 661) concluded that there can be no direct relation between neoplastic activity of hydrocarbons and their reactivity towards free radicals.

By 1950 it had become clear that the autoxidation of benzaldehyde can be retarded both by certain polycyclic hydrocarbons and by some of the quinones derived from them (cf.

* Part V, *J.*, 1953, 2993.

Part V, *loc. cit.*). In order to provide a much wider basis for tracing possible connections between carcinogenesis and the retardation of free-radical oxidations by polycyclic aromatic hydrocarbons and their various oxidation products it was then decided to make a fuller study of the whole subject. The kinetics of the retardation of benzaldehyde autoxidation by anthracene and by 1 : 2-5 : 6-dibenzanthracene have therefore been studied by us in some detail and a more general survey has been made of the behaviour of 16 other hydrocarbons, using the experimental methods of preceding Parts of this series of papers : the results are summarised below.

1. *Kinetics of Retardation of Autoxidation by Anthracene and by* 1 : 2-5 : 6-*Dibenzanthracene.*—For the benzoyl peroxide-initiated reaction at 60° it has been found that for both hydrocarbons the initial rate of oxygen uptake is proportional to

$$[\text{Benzoyl Peroxide}] \times ([\text{Benzaldehyde}] + a)/([\text{Hydrocarbon}] - b)$$

The two constants a and b are very small indeed in the case of anthracene and within the limits of experimental error in the case of dibenzanthracene. Moreover, in the pressure

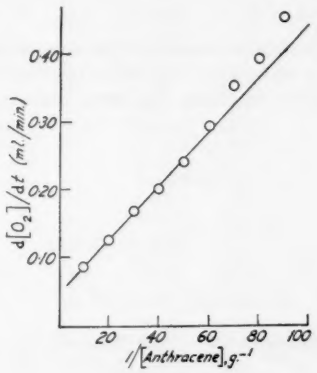


FIG. 1. *The retardation of benzaldehyde autoxidation by anthracene.*

Each mixture contained 1·00 *g. of benzoyl peroxide and* 1·50 *g. of benzoic acid in* 10 *ml. of benzaldehyde.*

range 20—76 cm. Hg, the initial oxidation rate is independent of the oxygen pressure. With anthracene these relations hold only at high relative concentrations of inhibitor and low concentrations of initiator; under reverse conditions higher oxidation rates are found (see Fig. 1 and Table 4, p. 585), for the rate of destruction of hydrocarbon molecules is then such that their mean concentration in the system during the 12-minute period of observation is noticeably less than the initial concentration. Since 1 : 2-5 : 6-dibenzanthracene is a much less efficient inhibitor it was used in higher concentration and consequently no corresponding deviations from regularity could be observed. As explained in Parts I and III of this series (*J.*, 1951, 812; 1952, 2427), if it is assumed that initially all the benzaldehyde–oxygen reaction chains are terminated by reactions involving hydrocarbon molecules, then *only* the following kinetic scheme accords with the experimental observations:

$$\text{Ph·CO·O–O·CO·Ph} \xrightarrow{k_1} 2\text{Ph·CO·O·}$$

$$\text{Ph·CO·O·} + \text{Ph·CHO} \xrightarrow{k_2} \text{Ph·CO}_2\text{H} + \text{Ph·CO·}$$

$$\text{Ph·CO·} + \text{O}_2 \xrightarrow{k_3} \text{Ph·CO·O·O·}$$

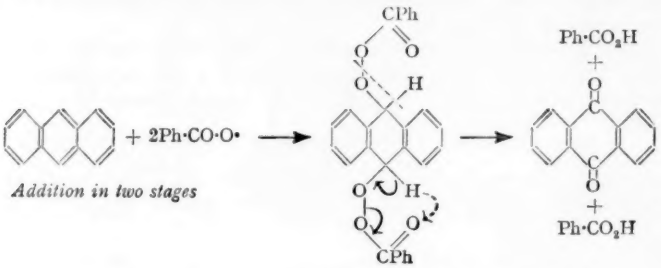
$$\text{Ph·CO·O·O·} + \text{Ph·CHO} \xrightarrow{k_4} \text{Ph·CO·O·OH} + \text{Ph·CO·}$$

$$\text{Ph·CO·O·O·} + \text{Hydrocarbon} \xrightarrow{k_5} \text{Inert products}$$

whence $$-\text{d}[\text{O}_2]/\text{d}t = 2k_1[(\text{Ph·CO}_2)_2](1 + k_4[\text{Ph·CHO}]/k_5[\text{Hydrocarbon}])$$

Direct abstraction of hydrogen atoms from hydrocarbon molecules would leave radicals active enough to effect chain transfer, and this would be inconsistent with the observed

kinetics. It seems likely therefore that the benzoylperoxy-radicals *combine* with the hydrocarbon to give the chain-ending reaction product. Direct evidence of radical addition to the 9- and the 10-position of anthracene has been obtained by Bickel and Kooyman (*Rec. Trav. chim.*, **1952**, **71**, 1137) using 2-cyano-2-propyl radicals and by Fieser and Putnam (*J. Amer. Chem. Soc.*, **1947**, **69**, 1038) using acetate radicals. It may be suggested that quinone formation occurs as follows:



Until direct measurements of the rate of destruction of hydrocarbon have been made it is not possible to be sure that other reactions do not occur. Clear evidence of the occurrence of consecutive reactions has been obtained by studying the retarded autoxidations over

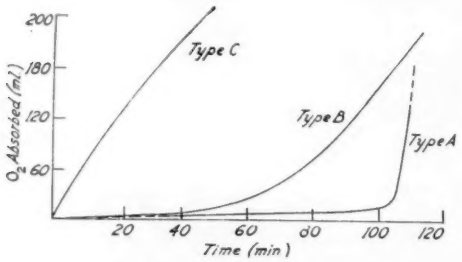


FIG. 2. *Types of retarded autoxidation curves* (*cf. Table* 1).

Curve A, plotted from data for anthracene.
Curve B, plotted from data for 20-methylcholanthrene.
Curve C, plotted from data for chrysene.

longer periods, with high catalyst : inhibitor ratios (see below), and in the case of 1 : 2-5 : 6-dibenzanthracene by investigating the nature of the final reaction product. In this instance the percentage yield of dibenzanthraquinone was very low, indicating that secondary reactions between quinone molecules and free radicals must occur.

2. *Types of Inhibiting Action shown in Prolonged Autoxidations.*—When the hydrocarbon retardation of the catalysed benzaldehyde autoxidation is examined over long periods of time, distinctive features of late stages of the reaction can be noted. From these it is evident that polycyclic aromatic hydrocarbons can, in general, be classified into three groups according to the type of oxygen uptake curve which can be obtained (*A*, *B*, and *C* of Fig. 2).

Class *A* includes those hydrocarbons which, though non-carcinogenic, are powerful inhibitors of autoxidation. Their oxygen uptake curves indicate that their oxidation products are incapable of inhibiting benzaldehyde autoxidation. Anthracene is a typical member of this group.

Class *B*, which includes the majority of the carcinogenic hydrocarbons, comprises the inhibitors which yield reaction products that also have inhibiting powers: 3 : 4-benzopyrene can be taken as typical of this class.

Class *C* comprises the weak inhibitors which became converted into oxidation products which have greater inhibiting power, so that the retardation of autoxidation becomes more evident after a long reaction period. This class includes chrysene, which is feebly carcinogenic (Steiner and Falk, *Cancer Res.*, **1951**, **11**, 56), and also the more powerful carcinogens 2-methyl-3 : 4-benzophenanthrene and 1 : 2-3 : 4-dibenzophenanthrene. Pyrene is anomalous, for its marked inhibiting action varies but little with time over a remarkably long

period (see below). In broad outline therefore carcinogenic action does seem to be associated with hydrocarbons which, of themselves or *via* their oxidation products, can exert some inhibiting action upon benzaldehyde autoxidation over a prolonged period.

Table 1 lists the types of autoxidation curve found for each hydrocarbon examined, together with the initial and the final autoxidation rates, measured under standard conditions. Each sample was tested at 60° in 10 ml. of benzaldehyde containing 1·5 g. of benzoic acid and 0·1500 g. of pure benzoyl peroxide as catalyst. Series I contained inhibitor molecularly equivalent to 0·005 g. of anthracene, series II an amount equivalent to 0·010 g., and series III an amount equivalent to 0·0150 g. Further consideration is given below to the data of series II of this Table.

TABLE 1.

Hydrocarbon	Type of curve	Series I. $-d[O_2]/dt$ init.	Series I. $-d[O_2]/dt$ max.	Series II. $-d[O_2]/dt$ init.	Series II. $-d[O_2]/dt$ max.	Series III. $-d[O_2]/dt$ init.	Series III. $-d[O_2]/dt$ max.
Anthracene	*A*	0·12	—	0·06	—	v. small	—
9-Methylanthracene	*A*	0·38	—	0·12	—	0·13	—
Naphthacene	*A*	—	—	—	—	—	—
5 : 6-*cyclo*Pentano-1 : 2-benzanthracene	*B*	0·447	14·7	0·149	8·99	0·097	5·8
1 : 2-Benzanthracene	*B*	1·04	17·0	0·42	8·2	0·19	4·3
10-Methyl-1 : 2-benzanthracene	*B*	1·31	9·18	0·419	9·1	0·216	5·9
5-Methyl-1 : 2-benzanthracene	*B*	0·93	18·6	0·33	8·0	0·12	5·2
10-*iso*Propyl-1 : 2-benzanthracene	*B*	6·73	16·2	1·39	11·04	0·828	8·08
1 : 2-7 : 8-Dibenzanthracene	*B*	1·30	7·8	0·58	4·1	0·35	2·8
3′-Methyl-1 : 2-5 : 6-dibenzanthracene	*B*	1·22	5·6	0·50	2·6	0·26	1·6
1 : 2-5 : 6-Dibenzanthracene	*B*	1·82	10·7	0·79	5·1	0·55	2·7
Pyrene	*C*?	0·44	—	0·226	—	0·14	—
2-Methyl-3 : 4-benzophenanthrene	*C*	8·44	—	3·84	—	2·84	—
1 : 2-3 : 4-Dibenzophenanthrene	*C*	13·3	—	5·37	—	3·39	—
Chrysene	*C*	10·8	—	6·35	—	4·84	—
Phenanthrene	*C*	—	—	v. large	—	—	—
3 : 4-Benzopyrene	*B*	0·155	—	0·081	2·3	0·051	1·3
20-Methylcholanthrene	*B*	0·37	15·1	0·098	4·7	0·061	3·5

$-d[O_2]/dt$ is given in ml. per min. (S.T.P.) per 10 ml. of benzaldehyde.

3. *Efficiency of the Initial Retardation of Autoxidation.*—If the kinetic equation of Section 1 above can be applied to the other polycyclic hydrocarbons, then since

$$k_5[\text{Hydrocarbon}] = \text{Constant}(-d[O_2]/dt - 2k_1[(Ph{\cdot}CO_2)_2])^{-1}$$

where k_1 is approximately 7×10^{-5} min.$^{-1}$ (cf. Bawn and Mellish, *Trans. Faraday Soc.*, 1951, **47**, 1216), relative values of k_5 can be computed from the simplified equation

$$k_5[\text{Hydrocarbon}] = \text{Constant}(-d[O_2]/dt - 0{\cdot}002)^{-1}$$

where $-d[O_2]/dt$ is measured in ml. per minute per 10 ml. sample of benzaldehyde.

Kooyman and Farenhorst (*Trans. Faraday Soc.*, 1953, **49**, 58), who measured the potencies of hydrocarbon inhibitors towards combination with trichloromethyl radicals, have satisfactorily correlated the logarithms of their reactivities with computed values of the maximum free valency numbers, $F_{max.}$, of their hydrocarbons. The velocity constants k_5 above may similarly be related to maximum free valency numbers, and Table 2 has been constructed on this basis. It is supposed that for those hydrocarbons in which there is more than one position of maximum free valency the reactivity of only one of the equivalent positions should be related to $F_{max.}$, and the reactivity of a hydrocarbon for radicals has therefore been computed as

$$R = \{n(-d[O_2]/dt - 0{\cdot}002)\}^{-1}$$

where n is the number of positions of maximum free valency.

Following Coulson, Burkitt, and Longuet-Higgins (*Trans. Faraday Soc.*, 1951, **47**, 553), $F_{max.} = N_{max.} - N_r$, where $N_{max.}$ for a carbon atom bound only to two others, as in these polycyclic aromatic hydrocarbons, has the value of $(3 + \sqrt{2})$, and N_r is the sum of the orders of all bonds joining the atom r to the remainder of the system. Computations by earlier theorists, who had chosen other values for $N_{max.}$, have been corrected to this scale. The

data for K_R given in Table 2 are the relative reactivity values found experimentally by Kooyman and Farenhorst.

Fig. 3 gives a plot of log R against $F_{max.}$ for those hydrocarbons for which theoretical calculations of free valency numbers have been made. It affords striking support for the view of Kooyman and Farenhorst that the maximum free valency number of a hydrocarbon is a valid measure of its reactivity towards free radicals. Consequently the experimental data given in Table 2 could be used to indicate the maximum free valency numbers of hydrocarbons for which computations have not yet been made, as for instance those containing alkyl substituents. Thus the maximum free valency number of 20-methylcholanthrene should be *ca.* 0·21, *i.e.*, slightly less than that for 3 : 4-benzopyrene and decidedly greater than those for 1 : 2-benzanthracene or for the dibenzanthracenes.

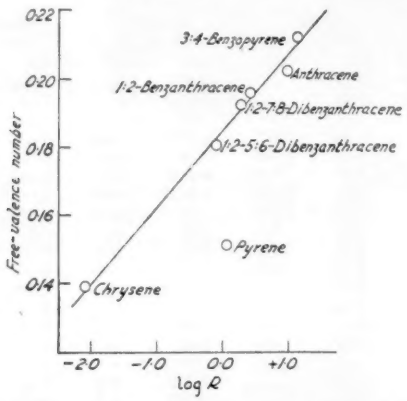


FIG. 3. *The connection between* log R *and* $F_{max.}$.

The only hydrocarbon having a much greater reactivity than would have been predicted is pyrene. Its strong inhibiting action has previously been reported by Lisle (*loc. cit.*) and by Wittig and Pieper (*Annalen*, 1947, **558**, 207). Under conditions in which anthracene was completely oxidised to the quinone, the latter workers were able to recover pyrene

TABLE 2. *The relation between retardation of autoxidation and* $F_{max.}$.

Hydrocarbon	n	$-d[O_2]/dt$	R	K_R	$F_{max.}$
3 : 4-Benzopyrene	1	0·081	12·99	70·0	0·212 [1]
20-Methylcholanthrene	1	0·098	10·64	48·8	—
Anthracene	2	0·059	9·09	11·0	0·202 [2]
9-Methylanthracene	1	0·120	8·62	—	—
5 : 6-*cyclo*Pentano-1 : 2-benzanthracene	1	0·149	6·90	—	—
5-Methyl-1 : 2-benzanthracene	1	0·33	3·07	—	—
10-Methyl-1 : 2-benzanthracene	1	0·42	2·41	—	—
1 : 2-Benzanthracene	1	0·42	2·40	20·0	0·196 [3]
3′-Methyl-1 : 2-5 : 6-dibenzanthracene	1	0·50	2·02	—	—
1 : 2-7 : 8-Dibenzanthracene	1	0·58	1·74	—	0·192 [4]
10-*iso*Propyl-1 : 2-benzanthracene	1	1·39	0·72	—	—
1 : 2-5 : 6-Dibenzanthracene	2	0·79	0·637	1·85	0·180 [4]
Pyrene	4	0·226	1·13	0·3	0·151 [3]
2-Methyl-3 : 4-benzophenanthrene	?3	3·84	?0·087	—	—
1 : 2-3 : 4-Dibenzophenanthrene	?4	5·37	?0·047	—	—
Chrysene	2	6·35	0·0435	$3·3 \times 10^{-2}$	0·139 [3]
Phenanthrene	4	v. large	v. small	$4·0 \times 10^{-2}$	0·134 [2]

[1] Kooyman and Farenhorst, *loc. cit.* [2] Coulson, Burkitt, and Longuet-Higgins, *loc. cit.* [3] Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906. [4] Baldock, Berthier, and Pullman, *ibid.*, 1949, **228**, 931.

unchanged at the end of an autoxidation. Its action, which remains obscure, may therefore have no relevance to the radical-combination process to which we have attributed the inhibiting actions of all the other hydrocarbons tested. In contrast to this, 1 : 2-benzanthracene, which Kooyman and Farenhorst thought to be anomalous, exhibits the expected degree of reactivity.

From Fig. 3 it can be deduced that a decrease of 0·01 in $F_{max.}$ corresponds to about a threefold decrease in the rate of radical combination at the position under consideration. Such a relation should also hold for the various $F_{max.}$ values at different positions within one hydrocarbon, and inspection of calculated F values shows that they differ sufficiently to justify the hypothesis of exclusive reaction at the point of maximum free valency.

4. *The Final Retardation of Benzaldehyde Autoxidation.*—Curve *B* of Fig. 2 indicates that the primary reaction products of the autoxidations of the carcinogenic hydrocarbons are themselves retarders of autoxidation. A measure of the efficiency of the retarding actions of these products is given by the slopes of the steeper, secondary parts of the autoxidation curves. In the case of 3 : 4-benzopyrene this may measure the inhibiting power of the toxic benzopyrenequinones: in the case of anthracene inhibition ceases entirely since the oxidation product, anthraquinone, is inert, while in that of 1 : 2-5 : 6-dibenzanthracene definite inhibiting power remains. Earlier work (Part V, *loc. cit.*) indicated that there was some connection between inhibiting powers of quinones and oxidation–reduction potentials. Iball (*Amer. J. Cancer*, 1940, **38**, 372) has measured the redox potentials of a number of benzanthraquinones, and Table 3 which gives his values indicates that there is some connection between the final autoxidation rates found for certain of the hydrocarbons and the redox potentials of the related quinones. The greater the redox potential of the final quinone the more is the retardation of the autoxidation of benzaldehyde after the initial action due to the chain-stopping by the hydrocarbon itself has ceased.

TABLE 3. *Suggested influences of quinones on final autoxidation rates.*

Hydrocarbon	$-d[O_2]/dt$ (max.)	π_0 for Quinone
1 : 2-5 : 6-Dibenzanthracene	3·70	0·255
1 : 2-7 : 8-Dibenzanthracene	3·57	0·238
1 : 2-Benzanthracene	2·33	0·224
5 : 6-*cyclo*Pentano-1 : 2-benzanthracene	1·77	0·173
5-Methyl-1 : 2-benzanthracene	1·92	0·168
Anthracene	0·00	0·150

We suggest that the general results discussed above have some relevance to the problem of carcinogenicity, but do not feel that our correlations can, as yet, do more than support the suggestion made under Section 2 of this discussion.

EXPERIMENTAL

Materials.—Anthracene was purified by Fieser's method ("Experiments in Organic Chemistry," D. C. Heath & Co., Boston, U.S.A., 1941, p. 345 footnote); commercial 1 : 2-5 : 6-dibenzanthracene (Messrs. L. Light & Co.) was crystallised to m. p. 261—262° after reaction with maleic anhydride (Cook *et al.*, *Proc. Roy. Soc.*, 1932, *B*, **111**, 469); pure pyrene was prepared for us at the laboratories of the Coal Tar Research Association, Gomersal, and the specimens of the carcinogenic hydrocarbons and their analogues were tested materials from the collection of the Chester Beatty Research Institute of the Royal Cancer Hospital.

The purifications of the benzaldehyde and benzoyl peroxide, and the kinetic measurements, were carried out as described in Part I, 60° being chosen for all comparative reactivity tests.

Kinetics of Retardation by Anthracene.—(i) Fig. 1 shows the variation of rate with concentration of anthracene. It can be seen that the initial rate, measured as the average for the first 12 min., increases unduly when the anthracene concentration is particularly low.

(ii) *Variation in benzoyl peroxide concentration.* Each mixture contained 1·50 g. of benzoic acid and 0·010 g. of anthracene in 10 ml. of benzaldehyde. The definite enhanced increase in reaction velocity at high benzoyl peroxide concentrations may be noted from Table 4.

TABLE 4.

Benzoyl peroxide (g.)	$-d[O_2]/dt$ (ml./min.)	$-[Bz_2O_2]d[O_2]/dt$	Benzoyl peroxide (g.)	$-d[O_2]/dt$ (ml./min.)	$-[Bz_2O_2]d[O_2]/dt$
0·2	0·083	0·415	0·8	0·328	0·410
0·3	0·137	0·443	0·9	0·388	0·431
0·4	0·154	0·385	1·0	0·457	0·457
0·5	0·205	0·410	1·1	0·503	0·462
0·6	0·243	0·405	1·2	0·631	0·526
0·7	0·272	0·389			

(iii) *Variation in benzaldehyde concentration.* Each system contained 1·000 g. of benzoyl peroxide, 0·010 g. of anthracene, 1·50 g. of benzoic acid, and 10·0 ml. of a benzaldehyde–chlorobenzene mixture. For ten rate determinations, with proportionate amounts from 1 to 10 ml. of benzaldehyde, the results could be expressed as

$$-d[O_2]/dt - 0{\cdot}1 = 36{\cdot}8 \times 10^{-3}, \pm 1{\cdot}07 \times 10^{-3} \text{ ml. of oxygen per min. per ml. of benzaldehyde present.}$$

(iv) *Variation in oxygen pressure.* Each system contained 0·300 g. of benzoyl peroxide, 0·005 g. of anthracene, and 1·50 g. of benzoic acid in 10 ml. of benzaldehyde. The following measurements were made at 80°, the absorption rates being calculated as ml. of oxygen at S.T.P. per min.

O_2 (mm.)	764	688	612	536	463	360	310	237	163
$-d[O_2]/dt$	0·255	0·264	0·255	0·269	0·267	0·249	0·250	0·229	0·241

Kinetics of Retardation by 1 : 2-5 : 6-*Dibenzanthracene.*—(i) *Variation in hydrocarbon concentration.* Each mixture contained 0·050 g. of benzoyl peroxide and 1·50 g. of benzoic acid in 10 ml. of benzaldehyde. For 8 determinations, with 6·0—50 mg. of hydrocarbon

$$-d[O_2]/dt \text{ (ml./min.)} \times [\text{Dibenzanthracene}] \text{ (mg.)} = 4{\cdot}32 \pm 0{\cdot}14$$

For this amount of benzoyl peroxide the calculated intercept is less than the experimental error.

(ii) *Variation in benzoyl peroxide concentration.* For 9 experiments, each with 0·050 g. of dibenzanthracene, and 1·50 g. of benzoic acid in 10 ml. of benzaldehyde and amounts of benzoyl peroxide varying from 30·4 to 600 mg.

$$(-d[O_2]/dt - 0{\cdot}018)/[\text{Benzoyl peroxide}] = 97{\cdot}0 \times 10^{-5} \pm 2{\cdot}8 \times 10^{-5} \text{ mg. ml./min.}$$

(iii) *Variation in benzaldehyde concentration.* Each mixture contained 0·5600 g. of benzoyl peroxide, 0·050 g. of dibenzanthracene, and 1·50 g. of benzoic acid in 10 ml. of a mixture of benzaldehyde and chlorobenzene. For 8 experiments, with from 1—10 ml. of benzaldehyde

$$(-d[O_2]/dt - 0{\cdot}022)/[\text{Benzaldehyde}] = 59{\cdot}0 \times 10^{-3} \pm 0{\cdot}85 \times 10^{-3} \text{ ml. of } O_2 \text{ per min.}$$

(iv) *Variation in oxygen pressure.* Each mixture contained 0·050 g. of benzoyl peroxide, 0·0070 g. of dibenzanthracene, and 1·50 g. of benzoic acid in 10 ml. of benzaldehyde.

O_2 pressure (mm.)	333	401	423	539	752
$-d[O_2]/dt$ (N.T.P.)	0·65	0·57	0·61	0·65	0·68

(v) *Oxidation products.* Air was aspirated for 36 hr. through a solution of dibenzanthracene (0·75 g.) and benzoyl peroxide (1·00 g.) in benzaldehyde (60 ml.) at 80°. Acids were removed by extraction with sodium hydrogen carbonate solution; no phenols could be removed by subsequent extraction with aqueous sodium hydroxide. The neutral remainder, after removal of benzaldehyde, was a dark red gum (1·73 g.) from which the only pure product which could be isolated chromatographically was 1 : 2-5 : 6-dibenzanthra-9 : 10-quinone, m. p. and mixed m. p. 248—249° (20 mg.).

The initial exploratory work, and the detailed study of 1 : 2-5 : 6-dibenzanthracene, were carried out by I.M.R., who thanks the British Empire Cancer Campaign for a Grant held during 1950—1952. J. R. D. thanks the Department of Scientific and Industrial Research for a Maintenance Grant held in 1951—1953. The authors thank Professors A. Haddow and F. Bergel of the Chester Beatty Research Institute for their help in providing most of the specimens of the hydrocarbons used in this investigation.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, October 6th,* 1953.]

Electron-transfer Reactions between Metallic Ions, Co-ordination Complexes, and Hæmoglobin.

By PHILIP GEORGE and D. H. IRVINE.

[Reprint Order No. 4676.]

Single-electron transfer reactions between (i) a simple aquated ion and a complex ion, and (ii) pairs of complex ions, are extremely rapid with velocity constants $k > 10^5$ l. mole^{-1} sec.$^{-1}$ in perchloric or nitric acid solution at 18°; the ions used were $Fe^{2+}_{aq.}$, $Ce^{4+}_{aq.}$, $IrCl_6^{2-}$, $Fe(CN)_6^{4-}$, $Mo(CN)_8^{4-}$, and the dipyridyl and phenanthroline complexes of Fe^{2+}, Fe^{3+}, Ru^{2+}, and Ru^{3+}. In 1·0M-sulphuric acid the reduction of ceric sulphate by $Ru(dipy)_3^{2+}$ or $Fe(5\text{-nitrophenanthroline})_3^{2+}$ is slower ($k \sim 4 \times 10^3$ l. mole^{-1} sec.$^{-1}$), but with $Fe(phen)_3^{2+}$ k is again $> 10^5$ l. mole^{-1} sec.$^{-1}$. These results are discussed in terms of the charge type of the reacting ions, and in relation to Libby's suggestion that activation energy may be required for the reorganisation of solvation or co-ordination shells which must necessarily accompany the electron transfer.

The transfer of two electrons in similar reactions involving $Tl^+_{aq.}$ and $Tl^{3+}_{aq.}$ is very much slower. The reduction of $Tl^{3+}_{aq.}$ by $Fe(phen)_3^{2+}$ has a velocity constant of about 7×10^{-3} l. mole^{-1} sec.$^{-1}$ at 25°, and data for this reaction are compared with those for the reduction by $Fe^{2+}_{aq.}$.

In phosphate buffer solutions of pH 6·0 hæmoglobin and its oxy- and carbonmonoxy-complexes (all ferrous protoporphyrin derivatives) are oxidised very rapidly by $IrCl_6^{2-}$ to methæmoglobin (the ferric protoporphyrin derivative). It is clear that the covalent bonding of the iron in the oxy- and carbonmonoxy-complexes does not "protect" it from oxidation. Cationic oxidising agents like $Ru(dipy)_3^{3+}$ are ineffective, apparently because other groups on the globin molecule are oxidised preferentially.

(A) *Single-electron Transfer between Metal Ions and Co-ordination Complexes.*—The investigation of exchange reactions between metal ions and complexes by use of radioactive isotopes is providing data of great value in understanding the factors governing the rate of electron-transfer reactions in general. Typical examples with their velocity constants are given in Table 1. Reactions of this type are of particular interest since the

TABLE 1. *Some electron-transfer reactions investigated by the radioactive-isotope method.*

Reactants	Velocity const. (l. mole^{-1} sec.$^{-1}$)	Ref.	Reactants	Velocity const. (l. mole^{-1} sec.$^{-1}$)	Ref.
Fe^{2+}, Fe^{3+}	~16	*a*	$Co(NH_3)_6^{2+}$, $Co(NH_3)_6^{3+}$	$< 6 \times 10^{-7}$	*c*
MnO_4^{2-}, MnO_4^-	>15	*b*	* $Fe(Me_2phen)_3^{2+}$, $Fe(Me_2phen)_3^{3+}$	$> 2 \times 10^4$	*d*
$Co(en)_3^{2+}$, $Co(en)_3^{3+}$	$5{\cdot}2 \times 10^{-5}$	*c*	$Fe(CN)_6^{4-}$, $Fe(CN)_6^{3-}$	$> 10^2$	*e*

* Me_2phen = 5 : 6-dimethylphenanthroline.

[a] Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 3315. [b] Adamson, *J. Phys. Coll. Chem.*, 1951, **55**, 293. [c] Lewis, Coryell, and Irvine, *J.*, 1949, S 386. [d] Eimer and Medalia, *J. Amer. Chem. Soc.*, 1952, **74**, 1592. [e] Cobble and Adamson, *ibid.*, 1950, **72**, 2276.

reactants are ions of similar charges, and electrostatic repulsion would be expected to result in negative entropies of activation and appreciable activation energies, possibly as high as 15 kcal./mole (Gorin, *J. Amer. Chem. Soc.*, 1936, **58**, 1787). Both of these features are present in some exchange reactions which have been found to proceed at conveniently measurable rates, *e.g.*, Tl^{3+}–Tl^+, V^{4+}–V^{3+}, Ce^{4+}–Ce^{3+}, and $Co(en)_3^{3+}$–$Co(en)_3^{2+}$; the activation energies range from 10 to 16 kcal./mole, and entropies of activation from about −16 to −32 e.u. (Harbottle and Dodson, *ibid.*, 1951, **73**, 2442; Furman and Garner, *ibid.*, 1952, **74**, 2333; Gryder and Dodson, *ibid.*, 1949, **71**, 1894; see also Table 1, ref. *c*). However, several exchange reactions proceed far faster than expected on this basis, particularly $Fe(CN)_6^{3-}$–$Fe(CN)_6^{4-}$ and Fe(dimethylphenanthroline)$_3^{3+}$–Fe(dimethylphenanthroline)$_3^{2+}$. The slight doubt as to whether the separation or diffusion procedures,

which have to be employed in the isotopic technique, themselves catalyse the exchange makes additional information on the speed of electron-transfer reactions between similarly charged ions of different species very desirable.

Taking advantage of the intense colour of many complex ions, easily detectable in 10^{-5}M-solutions, we examined the velocity of several such electron-transfer reactions, with the results recorded in Table 2.* All are fast reactions occurring " instantaneously " on

TABLE 2. *Reactions between one-electron transfer oxidising ions and one-electron transfer reducing ions, all of which are fast with velocity constants* $>10^5$ *l. mole*$^{-1}$ *sec.*$^{-1}$ *at about* 18°: S^+ *represents simple cation,* C^+ *or* C^- *a complex cation or anion.**

Type	Oxidising ion	E_0 (v)	Reducing ion	E_0 (v)	ΔE_0 (v)	ZZ'
$S^+ + C^-$	$IrCl_6^{2-}$	1·02	Fe^{2+}	0·77	0·25	− 4
$S^+ + C^+$	$Fe(phen)_3^{3+}$	1·14	Fe^{2+}	0·77	0·37	+ 6
	$Ru(dipy)_3^{3+}$	1·30	Fe^{2+}	0·77	0·53	+ 6
	Ce^{4+}	1·61	$Fe(dipy)_3^{2+}$	1·06	0·55	+ 8
	Ce^{4+}	1·61	$Fe(phen)_3^{2+}$	1·14	0·47	+ 8
	Ce^{4+}	1·61	$Ru(dipy)_3^{2+}$	1·30	0·31	+ 8
$C^+ + C^+$	$Fe(phen)_3^{3+}$	1·14	$Fe(dipy)_3^{2+}$	1·06	0·08	+ 6
	$Ru(dipy)_3^{3+}$	1·30	$Fe(dipy)_3^{2+}$	1·06	0·24	+ 6
$C^+ + C^-$	$Fe(phen)_3^{3+}$	1·14	$Fe(CN)_6^{4-}$	0·36	0·78	−12
	$Ru(dipy)_3^{3+}$	1·30	$Fe(CN)_6^{4-}$	0·36	0·94	−12
$C^- + C^-$	$IrCl_6^{2-}$	1·02	$Fe(CN)_6^{4-}$	0·36	0·66	+ 8
	$IrCl_6^{2-}$	1·02	$Mo(CN)_6^{4-}$	0·74	0·28	+ 8

* Reactions involving Ce^{4+} in 1·0M-$HClO_4$, all others in 10^{-3}M-HNO_3.

mixing of the solutions, which enables a lower limit for their velocity constants to be put at 10^5 l. mole^{-1} sec.$^{-1}$. Fast reactions between the oppositely charged ions are to be expected, but it is surprising that those between the similarly charged ions are also very fast. Nine of those listed in Table 2 come into this category, seven between cationic species and two between anionic species. These results substantiate the behaviour found in the $Fe(CN)_6^{3-}$–$Fe(CN)_6^{4-}$ and Fe(dimethylphenanthroline)$_3^{3+}$–Fe(dimethylphenanthroline)$_3^{2+}$ systems by the isotopic method, and in the $Os(dipy)_3^{3+}$–$Os(dipy)_3^{2+}$ exchange reaction by utilising the optical rotatory power of the stereoisomers. In this case Dwyer and Gyarfas (*Nature*, **1950**, **166**, 487) found the velocity constant at 10° to be about 10^3 l. mole^{-1} sec.$^{-1}$ by following the change in optical rotatory power when (+)- and (−)-stereoisomers of the Os^{3+} and Os^{2+} complexes respectively were mixed. Four of the fast reactions quoted in Table 2 are between pairs of similarly charged complex ions, so their speed cannot in part be accounted for through ion-pair complex formation of the type common in most exchange reactions between simple hydrated ions, an effect which reduces the charge product ZZ', *e.g.*, Cl^- catalysing the Fe^{3+}–Fe^{2+} and Eu^{3+}–Eu^{2+} exchanges *via* the ion-pair complexes $FeCl^{2+}$ and $EuCl^{2+}$ (Silverman and Dodson, *J. Phys. Chem.*, 1952, **56**, 846; Meier and Garner, *ibid.*, p. 853). The formation of conjugate acid species of the complex anions, *e.g.*, $HFe(CN)_6^{3-}$ from $Fe(CN)_6^{4-}$, would help to reduce the charge product in these systems, but an analogous reaction with the complex cations, *e.g.*, the production of $HFe(dipy)_3^{3+}$ from $Fe(dipy)_3^{2+}$ (Baxendale and George, *Trans. Faraday Soc.*, **1950**, **46**, 736) would lead to even greater discrepancies.

The extent to which these reactions proceed more rapidly than expected from their charge type can be seen by referring to Table 3, which gives activation energies, E, and temperature-independent factors, A, for several typical reactions between ions, including some of the more normal exchange reactions. The low A factors are fairly satisfactorily accounted for by sizable negative entropies of activation, ΔS^* ranging from −10 to −30 e.u./mole, arising from the electrostatic interaction (Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, New York, 1941, chapter 8). With a lower limit of 10^5 l. mole^{-1} sec.$^{-1}$ for the velocity constant of the reactions listed in Table 2,

* The rapid reaction between $Fe(phen)_3^{3+}$ and $Fe(dipy)_3^{2+}$ was previously reported by J. H. Baxendale and P. George at a discussion on " The Use of Radioactive Tracers in Chemistry " in London, April 1st, 1949, the main papers of which appear in *J.*, 1949, S 235; 420.

calculation shows that if A should have the value $1{\cdot}43 \times 10^{13}$, *i.e.*, $\Delta S^* = 0$, E is still less than 11·0 kcal./mole, whilst if A is put at $6{\cdot}5 \times 10^8$, *i.e.*, with a more reasonable value of −20 e.u./mole for ΔS^*, then E is less than 5·2 kcal./mole. It seems clear that in some way these electron-transfer reactions involving complex ions can occur more rapidly than similar reactions of aquated ions or reactions in which chemical bonds are broken and re-formed—for instance, the oxygen-atom transfer reaction at the top of Table 3.

TABLE 3. *Kinetic data for various reactions between similarly charged ions, including some from Table 2 for comparison where* S^{2+} *and* C^{3+}, *for instance, refer to a simple aquated ion and a complex ion, respectively.*

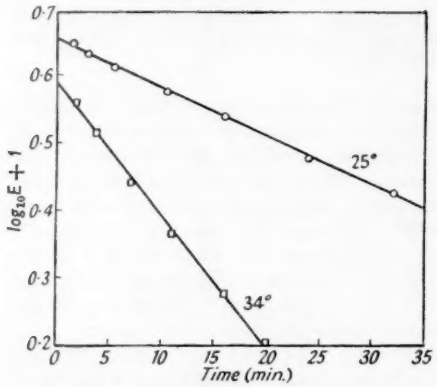
Reaction	ZZ'	Temp.	k, l. mole^{-1} sec.$^{-1}$	E, kcal./mole	A, l. mole^{-1} sec.$^{-1}$	Ref.
$AsO_3^{3-} + TeO_4^{2-}$	+ 6	89·6°	$3{\cdot}63 \times 10^{-3}$	14·4	$1{\cdot}7 \times 10^6$	*a*
$Co(NH_3)_5Br^{2+} + Hg^{2+}$	+ 4	25	3·3	12·3	$3{\cdot}5 \times 10^6$	*b*
$Co(en)_3^{3+} + Co(en)_3^{2+}$	+ 6	25	$5{\cdot}2 \times 10^{-5}$	~14·1	$1{\cdot}1 \times 10^6$	*c*
$VO^{2+} + VOH^{2+}$	+ 4	25	1	10·7	$1{\cdot}0 \times 10^5$	*d*
$Ce^{4+} + Ce^{3+}$	+12	25	16	13·4	$1{\cdot}1 \times 10^{11}$	*e*
$C^{3+} + S^{2+}$	+ 6	18	$>10^5$	<11·0 if A = $1{\cdot}43 \times 10^{13}$		
$S^{4+} + C^{2+}$	+ 8	18	$>10^5$			
$C^{3+} + C^{2+}$	+ 6	18	$>10^5$	<5·2 if A = $6{\cdot}5 \times 10^8$		
$C^{2-} + C^{4-}$	+ 8	18	$>10^5$			

[a] Stroup and Meloche, *J. Amer. Chem. Soc.*, 1931, **53**, 3331. [b] Bronsted and Livingston, *ibid.*, 1927, **49**, 435. [c] Lewis, Coryell, and Irvine, *J.*, 1949, S 386. [d] Furman and Garner, *J. Amer. Chem. Soc.*, 1952, **74**, 2333. [e] Gryder and Dodson, *ibid.*, 1949, **71**, 1894.

Although these reactions in 10^{-3}M-nitric acid and 1·0N-perchloric acid were too fast for kinetic measurements, some reactions of the ceric ion in sulphuric acid solution were slow enough: in 1·0M-acid the velocity constant for reduction by $Ru(dipy)_3^{2+}$ was approximately $4{\cdot}0 \times 10^3$ l. mole^{-1} sec.$^{-1}$ at 18°. With the 5-nitrophenanthroline complex of ferrous iron, the velocity constant was the same within experimental error, but with the unsubstituted phenanthroline complex $Fe(phen)_3^{2+}$ the reduction was again too fast for kinetic measurements. Moore and Anderson (*J. Amer. Chem. Soc.*, 1945, **67**, 167) showed that, at concentrations of less than 0·01M in ceric and sulphate ion in 2N-perchloric acid, the first ion-pair complex $CeSO_4^{2+}$ predominates with a formation equilibrium constant of 2×10^3 mole^{-1} at 24°, but that at higher concentrations other complex ions are formed with more sulphate bound. Hardwick and Robertson (*Canad. J. Res.*, 1951, **29**, 828) obtained values for the equilibrium constants of 3500, 200, and 20 for the successive formation of the species $CeSO_4^{2+}$, $Ce(SO_4)_2$, and $Ce(SO_4)_3^{2-}$ at 25° in solution of ionic strength 2·0. Thus in the present reduction experiments certainly less than 1 part in 2000, and probably as little as 1 part in 10^7, of the ceric ion is present as the simple aquated ion. From Hardwick and Robertson's values it follows that about 5% of the ceric ion is present as $Ce(SO_4)_2$ and 95% as $Ce(SO_4)_3^{2-}$. The slow reduction under these conditions is somewhat surprising in view of the widespread catalysis of electron transfer between metal ions by complex-forming anions, especially since the temperature-independent factor for reaction of $Ru(dipy)_3^{2+}$ with Ce^{4+} might be expected to be several powers of ten lower than that for its reaction with $Ce(SO_4)_3^{2-}$, where the reacting ions are of opposite charge.

These results are particularly interesting in connection with Libby's recent theoretical discussion of the factors governing the speed of electron transfer (*J. Phys. Chem.*, 1952, **56**, 863). They may be summarised thus: (i) Electron exchange between simple aquated ions like $Fe^{3+}_{aq.}$ and $Fe^{2+}_{aq.}$ is relatively slow, since it results in the production of a ferrous ion in the solvation environment of a ferric ion and *vice versa*, entailing activation energy to bring about the necessary rearrangement of the water molecules in the solvation shells. (ii) The magnitude of this activation energy is reduced if the ions form firm complexes so that both valency states are symmetrical and of the same dimensions to within the amplitude of the zero-point motion in the ground state. If this conditions holds, then no rearrangement of the co-ordination shell accompanies the transfer. (iii) In an exothermic oxidation–reduction between different species, the energy being liberated can lower the energy of activation otherwise required for the rearrangement of solvation and co-ordination shells.

Libby suggests that (i) and (ii) account for the slowness of the $Fe^{3+}_{aq.}$–$Fe^{2+}_{aq.}$ exchange compared with $Fe(CN)_6^{3-}$–$Fe(CN)_6^{4-}$. The speed of the reactions between complex ions listed in Table 2 would also follow from (ii) and (iii). However, the relative slowness of the $Os(dipy)_3^{3+}$–$Os(dipy)_3^{2+}$ exchange compared with the speed of the reaction between $Fe(phen)_3^{3+}$ and $Fe(dipy)_3^{2+}$, $Ru(dipy)_3^{3+}$ and $Fe(dipy)_3^{2+}$, etc., is surprising, for all these species apparently involve firm bonding in Libby's sense, like the $Fe(CN)_6^{4-}$ and $Fe(CN)_6^{3-}$ ions. This could be explained in terms of (iii) if activation energy were still an important consideration in these reactions, for whereas the exchange is thermoneutral, the reactions between the different complex ions are very likely to be exothermic, as a consideration of the entropy changes in relation to the overall free-energy decrease shows (see Baxendale and George, *loc. cit.*). In two cases, however, the exothermicity is not likely to be very large. In the $Fe(phen)_3^{3+}$–$Fe(dipy)_3^{2+}$ reaction it will be about 2 kcal./mole in view of the small difference in oxidation–reduction potential and the great similarity between the structures of the complex ions. Calculations, details of which are given later, suggest that the Ce^{4+}–$Ru(dipy)_3^{2+}$ reaction is also exothermic but only to the extent of 1·3—3·3 kcal./mole. This reaction is one where Libby's considerations would predict a relatively slow rate, since a cerous ion is formed in the unfavourable solvation



First-order plots for the reaction between thallic perchlorate and tris-o-phenanthrolineferrous perchlorate at 25° and 34° in 2·7M-$HClO_4$ solution. In each case the thallic perchlorate was in excess, $3·6 \times 10^{-2}$M being present compared with an initial concentration of the ferrous complex of about 5×10^{-5}M; E is the optical density of the solution at 510 mμ.

environment of the ceric ion: yet it is far faster than the Ce^{4+}–Ce^{2+} exchange. These two cases suggest that a small favourable free-energy or heat change can result in a great increase in the rate of the electron exchange. The possibility of small changes being significant in this way is borne out by a comparison of the speed of reduction of ceric sulphate by $Ru(dipy)_3^{2+}$, $Fe(5\text{-nitrophenanthroline})_3^{2+}$, and $Fe(phen)_3^{2+}$. Although the mechanism is obscure, the change in rate constant from about 4×10^3 to $>10^5$ l. mole^{-1} sec.$^{-1}$ can be correlated with the increasingly favourable free-energy change which has values of −3·2, −4·4, and −6·9 kcal./mole respectively; and in all probability, since the three complex ions have very similar structures, the exothermic heats of the reactions increase likewise.

Whatever the detailed physical mechanism of these reactions may be, it is abundantly clear that high charges of the same sign on the two reacting species do not necessarily entail slow electron transfer. There is, however, always the possibility that special features are present, such as far larger effective collision diameters, so that no strict comparison is possible with the behaviour observed in bond-breaking reactions.

(B) *Two-electron Transfer Reactions between a Metal Ion and Co-ordination Complexes.*—The other slow reactions of complex ions encountered in this investigation were those involving the Tl^{3+}–Tl^{+} couple, which requires the transfer of two electrons. The oxidation of Tl^{+} by $Ru(dipy)_3^{3+}$ in 0·5M-nitric acid is extremely slow, with a half-time of several hours at room temperature. The reduction of Tl^{3+} by $Fe(phen)_3^{2+}$ in perchloric acid solution is faster and the progress of the reaction can be followed easily (see Figure). The bimolecular velocity constant in 2·7M-perchloric acid at 25° is approx. $7·3 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. The

reaction has an apparent activation energy of about 20 kcal., and is faster in less acid solution, with a hydrogen-ion dependence of approximately inverse first power, indicating that a partly hydrolysed thallic ion is an important reacting species. This behaviour is in many respects similar to that found for the reduction of Tl^{3+} by simple aquated Fe^{2+} ions (Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 959), where the observed bimolecular velocity constant can be expressed as the sum of two terms appropriate to two paths the reaction can take. If h stands for the hydrogen-ion concentration, then

$$k_{obs.} = \frac{K_1 k_1}{K_1 + h} + \frac{k_2 K_2}{h} \frac{K_1}{K_1 + h}$$

Johnson identified the first term with the reaction between Fe^{2+} and $TlOH^{2+}$, where k_1 is the velocity constant and K_1 the equilibrium constant for the ionisation $Tl^{3+} + H_2O \rightleftharpoons TlOH^{2+} + H^+$, and the second term with the reaction between Fe^{2+} and TlO^+, where k_2 is the velocity constant and K_2 the equilibrium constant for the second ionisation $TlOH^{2+} \rightleftharpoons TlO^+ + H^+$. K_1, k_1, and k_2K_2 have the values $1{\cdot}43 \times 10^5$ exp. $(-5890/\boldsymbol{R}T)$ l. mole^{-1}, $4{\cdot}33 \times 10^{11}$ exp. $(-18{,}400/\boldsymbol{R}T)$ l. mole^{-1} sec.$^{-1}$, and $1{\cdot}89 \times 10^{14}$ exp. $(-22{,}060/\boldsymbol{R}T)$ sec.$^{-1}$, respectively. Calculation shows that under the above conditions used for the reduction by $Fe(phen)_3^{2+}$, simple ferrous ions would react preferentially with $TlOH^{2+}$ rather than with TlO^+, for the velocity constants have the values $9{\cdot}8 \times 10^{-3}$ and $3{\cdot}2 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$, respectively. There is very little difference therefore between the net velocity constant for reduction by simple ferrous ions and the $Fe(phen)_3^{2+}$ complex, *i.e.*, $13{\cdot}0 \times 10^{-3}$ and $7{\cdot}3 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. However, since in 2·7M-perchloric acid the factor $K_1/(K_1 + h)$ is close to unity, any marked hydrogen-ion dependence must arise through the second ionisation, and these exploratory experiments thus suggest that TlO^+ is the chief species reacting with the complex-ion reducing agent. The overall activation energy of 20 kcal. is close to that of 22·0 kcal. for the simple ferrous ion reacting with TlO^+. This is another example where the activation energy for the reduction of an ion is greater than that of the electron-exchange reaction which, for the Tl^{3+}–Tl^+ system, has a value of 14·7 kcal. (Harbottle and Dodson, *loc. cit.*). The different features which the reduction by the complex ion presents, particularly considerations of hydration energy and its transfer along the lines of Libby's theoretical discussion summarised above, make it a very interesting system for further investigation.

(C) *Electron-transfer Reactions of Hæmoglobin.*—We have recently shown (*Biochem. J.*, 1953, **53**, xxv; *Science*, 1953, **117**, 220) that the ferric forms of the hæmoproteins myoglobin and peroxidase can be oxidised by the single-electron transfer reagents $IrCl_6^{2-}$ and $Mo(CN)_8^{3-}$ to compounds having the redox properties of quadrivalent iron compounds. These appear to be identical in physical and chemical properties with the intermediate compounds formed by hydrogen peroxide and alkyl hydroperoxides, which were long considered to be the peroxide complexes, Fe_p^{3+}–O·OH and Fe_p^{3+}–O·OR, where Fe_p^{3+} denotes the ferriprotoporphyrin iron atom. Cationic oxidising agents of comparable or greater oxidising power like $Fe(phen)_3^{3+}$ and $Ru(dipy)_3^{3+}$ failed to give these compounds, so an examination of the oxidation of other hæmoprotein derivatives, where the more familiar valency change $Fe_p^{2+} \longrightarrow Fe_p^{3+}$ occurs, was undertaken.

TABLE 4. *Reaction of hæmoglobin and myoglobin derivatives with oxidising agents in* 0·04M-*phosphate buffer solution* (pH 6·0) *at room temperature.* (Fe_p^{2+} and Fe_p^{3+} represent the ferrous and ferric protoporphyrin iron atoms.)

Reactants	Hb, *i.e.*, Fe_p^{2+}	HbO_2, *i.e.*, $Fe_p^{2+}O_2$	HbCO, *i.e.*, $Fe_p^{2+}CO$	MetMb, *i.e.*, Fe_p^{3+}
$Fe(CN)_6^{3-}$	Fast	Fast	Slow, dissociation determines rate	No reaction
$IrCl_6^{2-}$	Fast	Fast	Fast	Fast (pH > 8)
$Ru(dipy)_3^{3+}$	Alternative reactions of the ruthenium complex ion occur with all four derivatives			

The results are given in Table 4, which includes for comparison the action of $Fe(CN)_6^{3-}$ well established by many biochemical studies. $IrCl_6^{2-}$ was found to oxidise all the ferrous derivatives, hæmoglobin, oxyhæmoglobin, and carbonmonoxyhæmoglobin, extremely

rapidly to methæmoglobin, the corresponding ferric compound, with velocity constants greater than 10^5 mole^{-1} sec.$^{-1}$. The further oxidation of methæmoglobin to its higher oxidation state, Fe_p^{IV}, was avoided by keeping the pH <7, for there is evidence that the effective redox potential of the Fe_p^{IV}–Fe_p^{3+} couple in such systems is hydrogen-ion dependent such that $IrCl_6^{2-}$ is not a sufficiently strong oxidising agent to effect this oxidation step in more acid solutions. For the same reason $Fe(CN)_6^{3-}$ at all pH values is too weak an oxidising agent to give the Fe_p^{IV} compound. In contrast, $Ru(dipy)_3^{3+}$ was without effect on all these ferrous derivatives, which suggests that other reducing groups in the protein react preferentially. Tyrosine, tryptophan, and cysteine were all found to reduce $Ru(dipy)_3^{3+}$ extremely rapidly. On the other hand, $IrCl_6^{2-}$ reacted relatively slowly with these amino-acids. The slow oxidation of tyrosine and tryptophan in proteins even by mild oxidising agents like $Fe(CN)_6^{3-}$ is well known from the work of Mirsky and Anson (*J. Gen. Physiol.*, 1936, **19**, 451). The different action of the strong cationic and anionic oxidising agents may therefore be attributed to competition reactions of this sort.

A comparison of the rates at which $IrCl_6^{2-}$ and $Fe(CN)_6^{3-}$ react with carbonmonoxy-hæmoglobin suggests that the reaction follows a different path in the two cases. It is generally accepted that $Fe(CN)_6^{3-}$ only reacts with free Hb according to the mechanism

$$HbCO\ (i.e.,\ Fe_p^{+2}CO) \overset{\text{Slow}}{\rightleftharpoons} Hb\ (i.e.,\ Fe_p^{2+}) + CO$$

$$Hb\ (i.e.,\ Fe_p^{2+}) + Fe(CN)_6^{3-} \xrightarrow{\text{Fast}} MetHb\ (i.e.,\ Fe_p^{3+}) + Fe(CN)_6^{4-}$$

in which the rate-determining step is the slow dissociation of HbCO. Good evidence for this comes from Millikan's study of the corresponding reaction with muscle hæmoglobin, *i.e.*, myoglobin, which may be denoted by Mb (*Proc. Roy. Soc.*, 1936, *B*, **120**, 366). The rate of oxidation of MbCO by ferricyanide was found to increase by only 60% for a ten-fold increase in ferricyanide concentration. On the basis that the rate at the lower concentration corresponded to the dissociation rate of MbCO, the equilibrium constant for the reaction $Mb + CO \rightleftharpoons MbCO$, calculated by using the value for the forward velocity constant, was numerically consistent with a direct determination of the equilibrium constant. Whilst the slight increase in rate as the ferricyanide concentration is increased may be evidence for some direct reaction between MbCO and $Fe(CN)_6^{3-}$, the far greater speed of the $IrCl_6^{2-}$ oxidation of HbCO compared with its dissociation rate is good evidence that a direct oxidation of the carbonmonoxy-compound as such is possible. This is significant because it shows that the covalent bonding of the iron in the carbonmonoxy-complex does not protect it against oxidation. The ready oxidation of ferrocytochrome-*c*, where the iron is also covalently bonded, affords another example with a hæmoprotein (Theorell, *J. Amer. Chem. Soc.*, 1941, **63**, 182), and many more can be found amongst co-ordination complexes of ferrous ion, *e.g.*, $Fe(dipy)_3^{2+}$ and $Fe(phen)_3^{2+}$. This conclusion is of importance with regard to the mechanism of the oxidation of hæmoglobin and myoglobin to their respective ferric states by molecular oxygen; for these reactions, which show extremely complicated kinetic behaviour, can in part be accounted for by a reaction scheme in which oxyhæmoglobin and oxymyoglobin, both of which also contain the iron covalently bound, are oxidised directly by some free-radical intermediate (George and Stratmann, *Biochem. J.*, 1952, **51**, 418).

According to the above equation the direct oxidation of HbCO should lead to the liberation of gaseous carbon monoxide. Evolution of the appropriate amount of gas was confirmed by an experiment using a Warburg manometer. The use of $IrCl_6^{2-}$ in this way offers a possible method for the gasometric estimation of HbCO similar to that of HbO_2, where oxidation by $Fe(CN)_6^{3-}$ can be used successfully because the dissociation step is extremely rapid.

Experimental

Dipyridyl- and Phenanthroline-ferrous Complexes.—These were prepared by accurately weighing ferrous sulphate to give the desired concentration, dissolving it in dilute acid, and adding the requisite amounts of 2 : 2′-dipyridyl and 1 : 10-phenanthroline respectively. The ferric derivatives were prepared from these by oxidation with lead dioxide and a little

concentrated nitric acid and filtering through a sintered-glass funnel to remove the excess of dioxide.

Dipyridyl Ruthenium Complex Chloride.—The bivalent salt was prepared according to Burstall (*J.*, 1936, 173), and a stock solution converted into the tervalent compound by the same procedure as above.

Potassium Molybdocyanide.—This was prepared by Willard and Thielke's method (*J. Amer. Chem. Soc.*, 1935, **57**, 2609). After three recrystallisations of the crude product, titration with potassium permanganate showed the sample to be about 99% pure. Stock solutions were accordingly made up by weight.

Thallic Perchlorate Solution.—This was made by diluting a solution of thallic hydroxide in 60% perchloric acid to a suitable concentration. The hydroxide was prepared according to the method of Sherrill and Haas (*ibid.*, 1936, **58**, 953). The thallic perchlorate was standardised with potassium bromate (Noyes *et al.*, *ibid.*, 1935, **57**, 1232).

Hæmoglobin Derivatives.—These were obtained from pure oxyhæmoglobin prepared from horse blood and purified according to Keilin and Hartree's method (*Proc. Roy. Soc.*, 1935, *B*, **117**, 1).

All other reagents used were of the highest analytical grades.

All the reactions mentioned in this paper involved a highly coloured reagent, so their rates could be followed by observing colour changes. In all cases, except in the reaction of thallic perchlorate with ferrous phenanthroline, a lower limit is given for the velocity constant. In these cases the reaction was instantaneous with the lowest convenient concentration of reactants, *viz.*, about 10^{-5}M. In this reaction the colour change of the ferrous complex at 510 mμ was followed by using a Unicam quartz spectrophotometer. The concentration of the thallic salt in these experiments was $3{\cdot}6 \times 10^{-2}$M, and that of the ferrous complex $5{\cdot}0 \times 10^{-5}$M. Under these conditions reasonably good first-order coefficients were obtained. Examples are given of runs at 25° and 34° (see Figure).

Except reactions involving ceric ion, which were carried out in approximately M-perchloric acid, all reactions were carried out in approximately 0·001M-nitric acid.

Calculation of Heat of Reaction between $Ce^{4+}_{aq.}$ *and* $Ru(dipy)_3^{2+}$.—The entropy change in the Ce^{4+}–Ce^{3+} cell reaction is +22·4 e.u., based on values for the partial molal entropies of $Ce^{4+}_{aq.}$ and $Ce^{3+}_{aq.}$ of −75·6 and −37·6 e.u. calculated from Powell and Latimer's empirical equation (*J. Chem. Phys.*, 1951, **19**, 1139) and 31·2 e.u. for the entropy of gaseous hydrogen. The oxidation reduction potential in about 1·0M-acid is 1·61 v for nitric acid and 1·70 v for perchloric acid. From these data ΔH for the cell reaction is found to be −30·5 and −32·5 kcal./mole, respectively.

The entropy change in the $Ru(dipy)_3^{3+}$–$Ru(dipy)_3^{2+}$ cell reactions may be assumed to be identical with that for the corresponding osmium complexes, *i.e.*, 2·6 e.u. as calculated from the data of Barnes, Dwyer, and Gyarfas (*Trans. Faraday Soc.*, 1952, **48**, 269). Its oxidation–reduction potential is 1·30 v (Dwyer, *J. Proc. Roy. Soc. N.S.W.*, 1949, **83**, 134), and hence ΔH for the cell reaction is −29·2 kcal./mole.

From these two ΔH values it follows that the electron-transfer reaction

$$Ce^{4+}_{aq.} + Ru(dipy)_3^{2+} \longrightarrow Ce^{3+}_{aq.} + Ru(dipy)_3^{3+}$$

is exothermic to the extent of about 1·3—3·3 kcal./mole.

Department of Colloid Science,
Free School Lane, Cambridge.

[*Received, September 25th*, 1953.]

β-*Acetylacrylic* (4-*Oxopent-2-enoic*) *Acid in the Diels–Alder Reaction. Part I. Some Derivatives of the Adduct derived from* β-*Acetylacrylic Acid and Butadiene.*

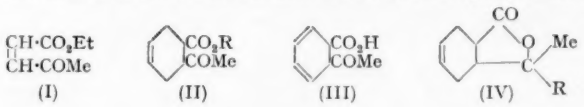
By S. Dixon and L. F. Wiggins.

[Reprint Order No. 4587.]

Ethyl β-acetylacrylate (4-oxopent-2-enoate), on being condensed with butadiene, furnished ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate; the corresponding acid is obtained by hydrolysis of this ester, and from β-acetylacrylic acid and butadiene. When the ester was treated with hydrazine and the product subjected to bromination and dehydrobromination, 1 : 2-dihydro-4-methyl-1-oxophthalazine, identical with the product of condensation of acetophenone-*o*-carboxylic acid with hydrazine, was isolated. 2-Acetyl-*cyclo*hex-4-ene-1-carboxylic acid yielded, by treatment with Grignard reagents, 5 : 5-substituted derivatives of hydro-1-oxo*iso*benzofuran. Three such showed no anthelmintic activity, but two others were slightly active against liver fluke.

Interest has developed recently in the synthesis of heterocyclic systems from sucrose. Thus, sucrose has been converted into derivatives of pyridazine (Wiggins *et al.*, *J.*, 1947, 239, 549; 1948, 2191, 2195, 2199; 1949, 1248, 2066, 2546; 1950, 3236, 3500, 3505, 3508), thiazole (Gregory and Wiggins, *J.*, 1947, 590, 1400), furan (Haworth and Jones, *J.*, 1944, 667; Haworth, Jones, and Wiggins, *J.*, 1945, 1; Newth and Wiggins, *J.*, 1947, 396; 1948, 155), and glyoxaline (Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 308), all except the last by way of lævulic acid or 5-hydroxymethylfurfuraldehyde both of which can be obtained from sucrose (Haworth and Wiggins, B.P. 591,858/1944). The present work concerns application of the Diels–Alder reaction to a derivative of lævulic acid namely, β-acetylacrylic (4-oxopent-2-enoic) acid (I), for the preparation of other cyclic derivatives. Formation of the acrylic acid derivatives from lævulic acid is well known and involves conversion of the latter into β-bromolævulic acid (Conrad and Guthzeit, *Ber.*, 1886, **19**, 1981) and dehydrobromination of this with sodium acetate (Wolff, *Annalen*, 1891, **264**, 247). Ethyl β-acetylacrylate is prepared similarly. Consistently good yields of these substances have been obtained by the modified procedures outlined by Overend, Turton, and Wiggins (*J.*, 1950, 3500).

Ethyl β-acetylacrylate (I) and butadiene in benzene at 100° under pressure gave, smoothly and in good yield, ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate (II; R = Et), a liquid characterised as its phenylhydrazone, thus providing a synthesis of a carbocyclic compound entirely from carbohydrate raw materials. Hydrolysis gave the corresponding crystalline acid (II; R = H) which was also prepared directly by addition of butadiene to β-acetylacrylic acid. In an attempt to obtain a *cyclo*hexadiene derivative, the acid (II; R = H) was converted into its dibromide and this was dehydrobrominated; however, only polymeric material was obtained in the latter reaction, and (III) could not be isolated.



(I) (II) (III) (IV)

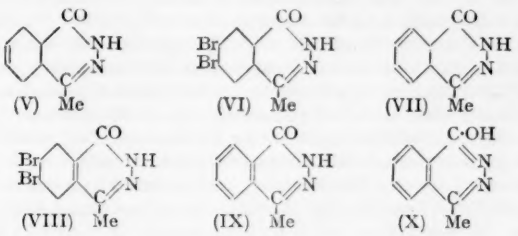
When 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid was heated above its melting point, water was evolved and after repeated distillation of the residue under atmospheric pressure a liquid, $C_9H_{10}O_2$, was isolated which will form the subject of a future communication.

The *cyclo*hexene keto-acid (II; R = H) might be expected to react with 3 mols. of methylmagnesium halide to yield a dialcohol. However, with 1 mol. or with an excess of the reagent, only the lactone (IV; R = Me) was obtained, in 67% and 69% yield, respectively. There seems no doubt that the starting material is an acid because of its analysis and since it behaves as an acid on titration and has pK 4·4; and the product must be (IV; R = Me) because of its analysis and titration as a lactone. Reaction with

1 mol. of Grignard reagent thus occurs preferentially (if not exclusively) with the keto-group rather than with the carboxyl group of the acid or the hydroxyl group of the intermediate alcoholic product; there appears to be no record of reaction of a keto-*acid* with a Grignard reagent and this merits further study. Formation of only the lactone, rather than the dialcohol, with an excess of methylmagnesium halide shows the preponderating influence of lactonisation in this reaction.

Although butyrolactone derivatives containing two alkyl, two aryl, or an alkyl and an aryl group at the carbon atom bearing the lactonic hydroxyl group show some activity as anthelmintics, three analogues of (IV; R = Me), *viz.*, (IV; R = Et, Ph, and *p*-MeO·C_6H_4), which were similarly prepared, had no useful activity; the 3 : 3-dimethyl (IV; R = Me) and the 3-methyl-3-phenyl compound (IV; R = Ph) in concentrations of 1 : 5000 reduced the activity of liver fluke, but not powerfully enough to counteract the stimulating effect of amphetamine.

2-Acetyl*cyclo*hex-4-ene-1-carboxylic acid or its ethyl ester readily condensed with hydrazine to form 1 : 2 : 5 : 8 : 9 : 10-hexahydro-4-methyl-1-oxophthalazine (V). This added one mol. of bromine in acetic acid, to form (VI), also obtained from 2-acetyl-4 : 5-dibromo*cyclo*hexane-1-carboxylic acid and hydrazine and converted by alkali into 1 : 2 : 9 : 10-tetrahydro-4-methyl-1-oxophthalazine (VII). When the dibromide (VI) was treated with a further mol. of bromine, dehydrogenation occurred with formation of (VIII) which was transformed by alkali into the aromatic benzo-derivative (IX or X); this was identical with the product of condensation of acetophenone-*o*-carboxylic acid with hydrazine.



Experimental

Condensation of Ethyl β-Acetylacrylate with Butadiene.—Ethyl β-acetylacrylate (4-oxopent-2-enoate) (5 g.) (Overend, Turton, and Wiggins, *J.*, 1950, 3500) was heated in a sealed tube at 100° for 4 hr. with a solution of butadiene (2 g.) in dry benzene (20 c.c.). Thereafter, the solvent was removed from the colourless solution, and the residual syrup (5·93 g.) fractionally distilled. After a small first fraction (b. p. 58—70°/0·02 mm.) which did not yield a crystalline phenylhydrazone, *ethyl 2-acetyl*cyclo*hex-4-ene-1-carboxylate* (4·0 g., 58%) distilled at 72°/0·02 mm. (Found: C, 67·4; H, 8·0. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%). The optimum yield (74%) was obtained by heating at 100° for 15 hr. The ester formed a crystalline *phenylhydrazone*, m. p. 107° (Found: C, 71·4; H, 7·8; N, 9·95. $C_{17}H_{22}O_2N_2$ requires C, 71·35; H, 7·7; N, 9·8%). It rapidly decolorized bromine in carbon tetrachloride with evolution of hydrogen bromide; after about 30 min. a solid was deposited, separation of which was completed by the addition of light petroleum. Recrystallized from alcohol–water, this furnished colourless needles of *ethyl 4 : 5-dibromo-2-bromoacetyl*cyclo*hexane-1-carboxylate*, m. p. 170—172° (Found: C, 29·9; H, 3·7. $C_{11}H_{15}O_3Br_3$ requires C, 30·3; H, 3·5%).

When the unsaturated ester (2 g.) was heated with 10% aqueous potassium hydroxide (25 c.c.) under reflux for 15 min. all the ester dissolved. The brown solution was allowed to cool, made slightly acid with dilute hydrochloric acid, and evaporated to dryness under reduced pressure. Extraction of the residue with boiling chloroform, evaporation, and recrystallization (charcoal) from alcohol–water or ether gave colourless prisms of *2-acetyl*cyclo*hex-4-ene-1-carboxylic acid* (1·45 g., 84·5%), m. p. 114—116° (Found: C, 64·3; H, 7·1. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%).

Condensation of β-Acetylacrylic Acid with Butadiene.—The acid (4·5 g.) (Overend, Turton, and Wiggins, *loc. cit.*) was heated in a sealed tube for 12 hr. at 100° with butadiene (3·5 g.) in dry benzene (20 c.c.) in the presence of quinol (0·5 g.). The light brown solution was then

concentrated to a syrup which rapidly crystallized. Crystallization from alcohol–water or ether gave colourless prisms of 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (4 g., 60·5%), m. p. 114—116°, identical with the product obtained as above. If the temperature was not allowed to exceed 100°, no polymerization inhibitor was needed, yields up to 83% being obtained.

Dry Distillation of 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylic Acid.*—The acid (1·0 g.) was heated in a distilling flask until distillation occurred, with dehydration (formation of water in the receiver). The colourless distillate was redistilled twice, dried ($MgSO_4$), and distilled once again, under reduced pressure. The *product* (0·7 g., 78%) was a mobile liquid, b. p. 168—170°/15 mm., n_D^{19} 1·5147 (Found: C, 71·5; H, 6·5. $C_9H_{12}O_2$ requires C, 71·9; H, 6·7%). A small amount of the product was dissolved in carbon tetrachloride and bromine added dropwise. Decolorization occurred and an oil separated. This solidified after several weeks and recrystallized from alcohol–water as colourless needles, m. p. 90°. It was a *dibromide* (Found: C, 34·9; H, 3·4. $C_9H_{10}O_2Br_2$ requires C, 34·9; H, 3·2%).

Addition of Bromine to 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylic Acid.*—(a) *At room temperature.* To the acid (1 g.) in dry ether (30 c.c.) bromine (1 g.) was added dropwise. Decolorization occurred and hydrogen bromide was eliminated. The precipitated solid 2-*acetyl*-4 : 5-*dibromo*-cyclo*hexane*-1-*carboxylic acid* crystallized from alcohol–water as needles (0·1 g., 5·1%), m. p. 170° (Found: C, 32·9; H, 3·8. $C_9H_{12}O_3Br_2$ requires C, 32·9; H, 3·7%). The filtrate, on evaporation under reduced pressure yielded a decomposed tar.

(b) On similar reaction at 0°, with continuous stirring, very little hydrogen bromide was evolved. Crystalline dibromide (0·85 g., 44%), m. p. 170° (from alcohol–water), separated when the solution was set aside.

Action of Alcoholic Potassium Hydroxide on 2-*Acetyl*-4 : 5-*dibromo*cyclo*hexane*-1-*carboxylic Acid.*—The dibromide (1·0 g.) was heated with potassium hydroxide (1·0 g.) in dry methyl alcohol (40 c.c.) on a water-bath for 3 hr. and then allowed to cool. No solid separated. After being made slightly acid with hydrochloric acid, the solution was evaporated to dryness and the residue extracted with chloroform. Evaporation of the extract yielded a viscid syrup (0·6 g.) which failed to crystallize, could not be distilled, and appeared to be polymeric. The same result was obtained when 1 mol. of potassium hydroxide was used.

Treatment of 2-*Acetyl*-4 : 5-*dibromo*cyclo*hexane*-1-*carboxylic Acid with Hydrazine Hydrate.*—The dibromide (0·5 g.) was heated with hydrazine hydrate (0·16 c.c., 50% aqueous solution) in methyl alcohol (15 c.c.) under reflux for 2 hr., concentrated to 5 c.c., and cooled. The solid which separated crystallized from alcohol–water as colourless plates (0·09 g., 18%), m. p. 194° (decomp.) alone or in admixture with 6 : 7-dibromo-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-octahydro-4-methyl-1-oxophthalazine (see below).

Action of Methylmagnesium Iodide on 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylic Acid.*—To the Grignard reagent prepared from methyl iodide (0·7 g.) and magnesium turnings (0·12 g.) in ether (2 c.c.) 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (0·75 g.) in ether (20 c.c.) was added dropwise. When the initial vigorous reaction had subsided, the mixture was heated under reflux on a water-bath for 3 hr. After being cooled, the ether was decanted from the complex and evaporated, yielding a negligible residue. The Grignard complex was decomposed with ice and dilute sulphuric acid. The precipitated solid 1 : 2 : 4 : 7 : 8 : 9-*hexahydro*-3 : 3-*dimethyl*-1-*oxoisobenzofuran* was separated and, recrystallized from alcohol–water, formed colourless plates (0·5 g., 67%), m. p. 114° (mixed m. p. with 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid, 72—80°) (Found: C, 72·3; H, 8·1. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·4%). Reaction with 4 mols. of Grignard reagent gave the same product, m. p. 114° in 69·5% yield.

Action of Other Grignard Reagents on 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylic Acid.*—To ethylmagnesium iodide (from ethyl iodide, 5·57 g. in ether), 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (1·5 g.) in dry ether (30 c.c.) was added. Heating for 2 hr. after the initial vigorous reaction, cooling, addition of dilute sulphuric acid, extraction of the aqueous layer several times with ether, drying ($MgSO_4$) and evaporation of the combined extracts yielded 3-*ethyl*-1 : 2 : 4 : 7 : 8 : 9-*hexahydro*-3-*methyl*-1-*oxoisobenzofuran* as a light brown oil (0·75 g.). This distilled as a colourless liquid, b. p. 175°/15 mm., n_D^{18} 1·4898 (Found: C, 73·1; H, 8·8. $C_{11}H_{16}O_2$ requires C, 73·4; H, 8·9%).

The Grignard reagent from bromobenzene (2·4 c.c.) and magnesium turnings (0·5 g.) in ether (8 c.c.), with 2-acetyl*cyclo*hex-4-ene-1-carboxylic acid (1·5 g.) in ether (30 c.c.), similarly gave the 3-*methyl*-3-*phenyl* compound as a dark brown oil which solidified during several days. Recrystallized from alcohol–water, it formed a colourless microcrystalline solid (0·65 g., 32%), m. p. 85° (Found: C, 78·8; H, 6·9. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·0%).

The Grignard reagent from *p*-methoxyphenyl bromide (6·8 g.) and magnesium turnings

(0·9 g.), with the acid (1·5 g.) in ether, similarly gave the 3-p-*methoxyphenyl*-3-*methyl* compound as needles (0·6 g., 26%; from alcohol–water), m. p. 145—147° (Found: C, 74·1; H, 7·1. $C_{16}H_{18}O_3$ requires C, 74·5; H, 7·0%).

Condensation of Ethyl 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylate with Hydrazine.*—The ester (6·0 g.) was mixed with 50% aqueous hydrazine solution (3·6 c.c.) and alcohol added until the mixture was homogeneous. The solution was then heated under reflux on a water-bath. After 15 min. a white crystalline solid began to separate, but heating was continued for 1 hr. After cooling, the solid was collected and, recrystallized from hot alcohol, formed long colourless needles of 1 : 2 : 5 : 8 : 9 : 10-*hexahydro*-4-*methyl*-1-*oxophthalazine* (4·8 g. 95·5%), m. p. 225—226° (Found: C, 65·7; H, 7·6; N, 17·1. $C_9H_{12}ON_2$ requires C, 68·85; H, 7·3; N, 17·1%).

Condensation of 2-*Acetyl*cyclo*hex*-4-*ene*-1-*carboxylic Acid with Hydrazine.*—The acid (7 g.) was dissolved in N-sodium hydroxide (42 c.c.) and cooled in ice. A cold solution of hydrazine sulphate (5·5 g.) in N-sodium hydroxide (42 c.c.) was carefully added and the mixture heated under reflux. After 10 min. crystals appeared. After being heated for 1 hr. the solution was allowed to cool, and the 1 : 2 : 5 : 8 : 9 : 10-hexahydro-4-methyl-1-oxophthalazine was collected, washed with water, and recrystallized from alcohol in long colourless needles (6·2 g., 88·5%), m. p. 225—226°, identical with the product described above.

Treatment of 1 : 2 : 5 : 8 : 9 : 10-*Hexahydro*-4-*methyl*-1-*oxophthalazine with Bromine.*—The oxophthalazine (4·0 g.), in hot glacial acetic acid (15 c.c.), decolorised bromine (4·0 g.; added dropwise) rapidly without elimination of hydrogen bromide. After about 10 min. a solid separated. After cooling, this was collected. It recrystallized from alcohol–water as colourless plates (0·8 g.), m. p. 194° (decomp.). The filtrate from the reaction mixture was concentrated under reduced pressure to a syrup which solidified on trituration with water. Recrystallized from alcohol–water, it formed colourless plates (3·9 g.), m. p. 194° (decomp.). The total yield of 6 : 7-*dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro*-4-*methyl*-1-*oxophthalazine* was 4·7 g. (59·5%) (Found: C, 33·4; H, 4·0; N, 8·8. $C_9H_{12}ON_2Br_2$ requires C, 33·4; H, 3·7; N, 8·7%).

Action of Alcoholic Potassium Hydroxide on 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro*-4-*methyl*-1-*oxophthalazine.*—The bromo-derivative (2·0 g.) was heated with potassium hydroxide (0·75 g.) in absolute alcohol (25 c.c.) under reflux for 5 hr. and the precipitated potassium bromide separated from the hot mixture. On being allowed to cool, the filtrate deposited crystalline 1 : 2 : 9 : 10-*tetrahydro*-4-*methyl*-1-*oxophthalazine* and a further crop was obtained from the mother liquor on concentration. It recrystallized from alcohol in long colourless needles (0·82 g., 82%), m. p. 223—224° (Found: C, 66·8; H, 6·3; N, 17·1. $C_9H_{10}ON_2$ requires C, 66·7; H, 6·2; N, 17·3%).

Dehydrogenation of 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8 : 9 : 10-*octahydro*-4-*methyl*-1-*oxophthalazine.*—The dibromide (1·5 g.) was dissolved, with stirring, in hot glacial acetic acid (25 c.c.), and bromine (0·75 g.) added dropwise. After a short time decolorisation occurred and hydrogen bromide was evolved. After all the bromine had been added, the solution was allowed to cool for about 30 min. and the precipitated solid was collected. Recrystallized from alcohol–water this formed colourless prisms (0·45 g., 30%) of 6 : 7-*dibromo*-1 : 2 : 5 : 6 : 7 : 8-*hexahydro*-4-*methyl*-1-*oxophthalazine*, m. p. 204° (Found: C, 34·0; H, 3·1; N, 8·9. $C_9H_{10}ON_2Br_2$ requires C, 33·5; H, 3·1; N, 8·7%).

Action of Alcoholic Potassium Hydroxide on 6 : 7-*Dibromo*-1 : 2 : 5 : 6 : 7 : 8-*hexahydro*-4-*methyl*-1-*oxophthalazine.*—The dibromo-compound (0·35 g.) was heated with potassium hydroxide (0·132 g.) in methyl alcohol (12·5 c.c.) under reflux for 30 min., then allowed to cool, and water (10 c.c.) was added. 1 : 2-Dihydro-4-methyl-1-oxophthalazine which separated was collected, washed with a little water, and crystallized from alcohol–water; it formed colourless needles (0·14 g., 80·5%), m. p. 222° alone or in admixture with an authentic specimen prepared by condensing acetophenone-*o*-carboxylic acid with hydrazine (Found: C, 67·7; H, 5·0; N, 17·7. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·0; N, 17·5%).

The authors gratefully acknowledge the financial assistance of the Colonial Products Research Council, the helpful interest of Sir John Simonsen, F.R.S., and the assistance of Dr. Marshall of the Department of Pharmacology of the University of Birmingham in carrying out the biological tests.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

THE DEPARTMENT OF SUGAR CHEMISTRY AND TECHNOLOGY,
IMPERIAL COLLEGE OF TROPICAL AGRICULTURE,
TRINIDAD, BRITISH WEST INDIES.

[*Received, August 14th,* 1953.]

A Spectroscopic Study of the Nature of the Complexes of Purines with Aromatic Compounds.

By J. Booth, E. Boyland, and S. F. D. Orr.

[Reprint Order No. 4642.]

The changes in infra-red absorption spectra observed on formation of crystalline complexes of caffeine and tetramethyluric acid with polycyclic hydrocarbons, dibenzocarbazoles, and other polycyclic aromatic compounds are only slight and comparable with those observed in the formation of the complex from diphenyl and 4 : 4′-dinitrodiphenyl by Burton and Richards (*J.*, 1950, 1316). They are, however, always in the same direction and can be related to structural changes; furthermore, comparable changes have been observed in concentrated chloroform solutions. These facts support the suggestion that the complexes owe their formation to forces of attraction between the two components arising from their mutual polarization.

The ability of purines such as caffeine to form complexes with many other substances has long been known, and that aqueous solutions of purines can dissolve carcinogenic hydrocarbons including 3 : 4-benzopyrene was shown by Brock, Druckrey, and Hamperl (*Arch. Exp. Path. Pharm.*, 1938, **189**, 709). The quantitative aspect of the solubilization of aromatic hydrocarbons (both carcinogenic and non-carcinogenic) by purines in aqueous solution was studied by Weil-Malherbe (*Biochem. J.*, 1946, **40**, 351), who also prepared crystalline molecular compounds of pyrene, 3 : 4-benzopyrene, and coronene with 1 : 3 : 7 : 9-tetramethyluric acid; the forces responsible for the two effects were postulated by him as probably identical.

The solubilizing effect of aqueous solutions of purines has also been shown with carcinogenic aromatic amines such as benzidine and aminofluorene by Neish (*Rec. Trav. chim.*, 1948, **67**, 361) and for carcinogenic dibenzacridines and dibenzocarbazoles by Booth and Boyland (*Biochim. Biophys. Acta*, 1953, **12**, 75). The latter authors also showed that polycyclic compounds were dissolved by aqueous solutions of sodium deoxyribonucleate. In some of these instances solid molecular compounds are also formed, having been reported for caffeine and 1 : 3 : 5 : 7-tetramethyluric acid with a variety of the above-mentioned aromatic compounds. The infra-red spectra of some of these solid complexes, and both infra-red and ultra-violet spectra of their solutions have been obtained. The complexes studied were those of 1 : 2-5 : 6, 1 : 2-7 : 8-, and 3 : 4-5 : 6-dibenzocarbazole α-naphthol, and benzidine with both caffeine and tetramethyluric acid, and of pyrene, 3 : 4-benzopyrene, β-naphthylamine, and 3 : 4-6 : 7-dibenzacridine with tetramethyluric acid.

Experimental

Preparation of Molecular Complexes.—The molecular complexes formed by tetramethyluric acid with pyrene and 3 : 4-benzopyrene were kindly given by Dr. H. Weil-Malherbe.

The other complexes were prepared by shaking an excess of the solid aromatic compound (or a small volume of concentrated ethanolic solution) in a saturated aqueous solution of the purine and filtering off the excess of solid. A small amount of crystalline material was precipitated on storage and was separated by filtration (Booth and Boyland, *loc. cit.*).

Infra-red Spectra.—These were obtained on a Perkin-Elmer 12C spectrometer fitted with a 13-cycle amplifier. The spectra from 3600 to 2500 cm.$^{-1}$ were obtained witha lithium fluoride prism, and from 1900 to 650 cm.$^{-1}$ with a rock-salt prism. The accuracy of band position, expressed as wave-length deviation, remained approximately constant over the entire region at about 0·01 μ, and the reproducibility of successive runs was within about 0·003 μ. Materials in the solid state were measured as mulls in liquid paraffin or, where that medium absorbed, in a fully fluorinated oil. Chloroform was used as solvent for measurements on solutions, which were made up as follows. Saturated solutions of these substances in chloroform are about 0·5M. The aromatic compound was therefore dissolved in an equivalent amount of 0·5M-purine solution and made up to a known volume, giving about a 0·35M-solution. With tetramethyluric acid, 3 : 4-5 : 6-dibenzocarbazole and α-naphthol dissolved, but within a minute

the solid complex was deposited from solution; from 0·12M-solution the carbazole complex was only slightly, and the α-naphthol complex not at all, precipitated. This precipitation is analogous to that observed in aqueous solutions by which method the majority of the complexes were prepared.

Ultra-violet Spectra.—Absorption measurements were made with a Unicam S.P. 500 photoelectric spectrophotometer, readings being taken at intervals of 1 mμ. The spectra of the molecular compounds and their components were measured in ethanol or benzene. For examination of the effect on the spectra produced by a large excess of purine, 50% ethanol was used in most cases.

Results and Discussion

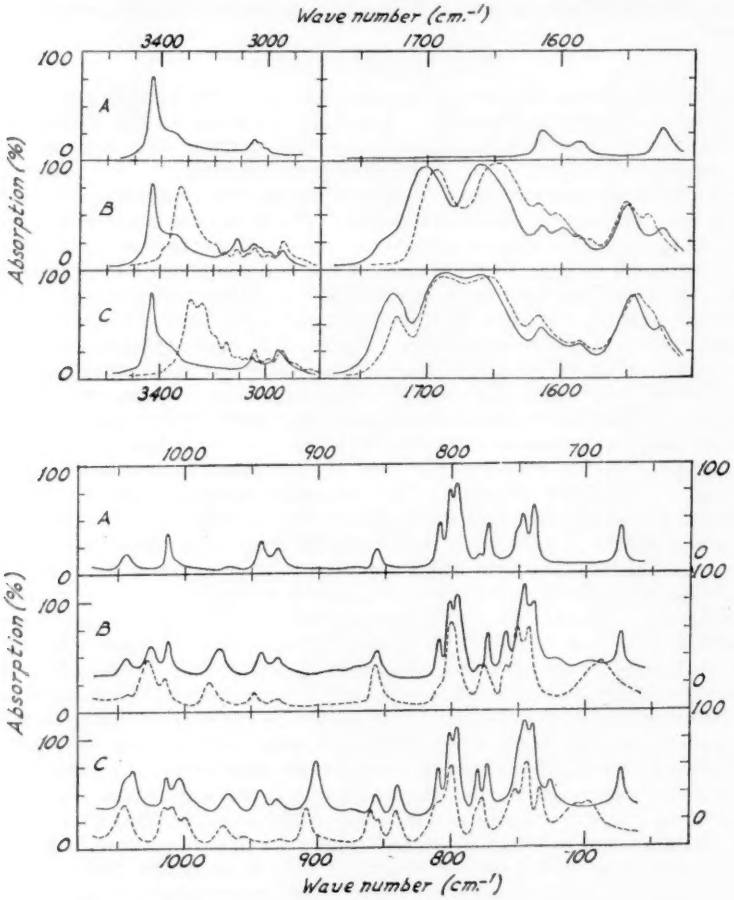
The infra-red spectra of the pure components and the fourteen complexes were measured as solids under the conditions described. A typical set is shown in Fig. 1 where the spectra of the complexes of 3 : 4-5 : 6-dibenzocarbazole with caffeine and tetramethyluric acid may be compared with those of the mixtures of their components. From the spectrum of pure 3 : 4-5 : 6-dibenzocarbazole, it can be seen which part of the absorption of the mixture is due to it and which to the respective purine. The changes in absorption are relatively small and are typical of the effect obtained in all cases. It was in order to facilitate observation of these small changes that mixtures of the two components in proportions corresponding to each complex were made up as mulls in liquid paraffin and compared with the corresponding complex. If kept, such mixtures invariably formed complexes after times varying from 30 minutes to several weeks. The reaction time was reduced by heating and appeared to depend mainly on other external factors such as the extent of grinding and the amount of moisture or impurities present. The change did not occur on grinding of the dry materials together but it was always effected by melting, and these facts suggest that, as expected, complex formation takes place in solution, even though limited as in the case of the liquid paraffin. In all except one case, the complexes formed in this and the more conventional manner were identical. The exception occurred with 1 : 2-5 : 6-dibenzocarbazole and tetramethyluric acid which gave a 1 : 2 complex on isolation from solution. Heating a synthetic 1 : 2 mixture in liquid paraffin suspension sometimes gave the same complex, sometimes another form which appeared to have excess of free tetramethyluric acid. Heating a synthetic 1 : 1 mixture in a similar way gave this form without the free acid, showing the formation of a stable 1 : 1 complex. On storage at room temperature or only gentle heating two further 1 : 1 complexes were formed; these were metastable, however, and could always be transformed into the stable one. These forms must have different crystal structures whose relative stability is dependent on the amount of interaction possible between the two components in the particular geometrical arrangement.

The spectral changes observed are of the same order as those observed by Burton and Richards (*loc. cit.*) for complexes between certain polarizable aromatic compounds and some strongly polar polynitro-compounds. These authors pointed out that similar shifts have been observed during changes of state in pure compounds, and concluded that the complexes owe their stability, not to forces of attraction between the components, but rather to the lower energy of their crystal lattices compared with those of the component materials. The fact that a closely related series of complexes has been examined has, however, shown that the shifts are not purely random and suggests that attractive forces, though small, do exist between the components. Thus, it was found that the bands for caffeine at 1701 and 1658 and for tetramethyluric acid at 1688 and 1659 cm.$^{-1}$, due to the C=O groups, are invariably reduced in frequency on complex formation, usually by 5—10 cm.$^{-1}$. Similarly the strong bands for caffeine at 1026 and 974 cm.$^{-1}$ and for tetramethyluric acid at 1003 and 901 cm.$^{-1}$ (and, less consistently, at 1039 cm.$^{-1}$), which are almost certainly due to the C–N bonds contiguous to the C=O groups, are shifted to higher frequencies by 4—7 cm.$^{-1}$. Again, the strong bands of the aromatic compound component at 750—850 cm.$^{-1}$, due to the out-of-plane C–H deformation modes, are invariably increased in frequency in the complex relative to their position in the parent; the increase averages about 8 cm.$^{-1}$, although in some cases it is about 12 cm.$^{-1}$.

Now these shifts are exactly those which would accompany the particular force of attraction between the two components postulated by Pauling (*Proc. Nat. Acad. Sci.*,

1939, **25**, 577) to explain the formation of complexes such as these between a polar and a polarizable molecule. This force of attraction is supposed to arise in the following way. The aromatic compounds have large polarizabilities in the planes of their molecules. Hence, a molecule of the polarizable component lying close to and parallel to one of the

FIG. 1. *Infra-red spectra as mulls in liquid paraffin or fully fluorinated oil in regions where differences are most marked between complexes and their components.*



A, ——— 3 : 4-5 : 6-*Dibenzocarbazole.*
B, ——— 1 : 1 *Mixture of* 3 : 4-5 : 6-*dibenzocarbazole and caffeine.*
– – – – *Corresponding complex.*
C, ——— 1 : 1 *Mixture of* 3 : 4-5 : 6-*dibenzocarbazole and tetramethyluric acid.*
– – – – *Corresponding complex.*

In B and C, from 1060 *to* 750 *cm.*$^{-1}$, *the curve of the mixture is displaced upwards corresponding to* 25% *absorption.*

polar molecules is polarized and stabilizes those structures of the polar molecule which bear separated charges. This increases their contribution to the resonance hybrid, and gives rise to an interaction potential corresponding to a force of attraction, thus explaining the formation of a stable complex. Furthermore, a modification of the electronic distribution in the molecules is involved and this should be detectable in their spectra; in particular, the C–O bonds of the purine have less, and the C–N bonds more, double-bond

character and the frequency of the bands in the infra-red characteristic of their stretching modes are respectively lowered and raised. These are indeed the directions of the small shifts observed and strongly suggest that an interaction of this type occurs. Briegleb (*Z. physikal. Chem.*, **1935**, **31**, *B*, 58) had suggested a similar theory, envisaging the polar molecule as inducing dipole moments in the polarizable one and the attraction resulting from the interaction of the permanent and the induced dipole.

If the formation of the solid complex is due to the type of interaction described above, the effect should be observed in solution. However, as the interaction is a short-range effect, one can only expect its detection in concentrated solutions. Chloroform was chosen as solvent; it dissolves either component to a reasonable extent and, in the 0·1-mm. thickness used, is sufficiently transparent to give the complete spectrum from 820 to 3600 cm.$^{-1}$ except for a narrow region at 1195—1245 cm.$^{-1}$. The interactions of 3 : 4-benzopyrene with tetramethyluric acid and of 3 : 4-5 : 6-dibenzocarbazole, α-naphthol and pyrene with both caffeine and the acid were studied in this solvent. The most concentrated solutions possible were used, and comparisons of the spectra were made between those of the mixed solutions and of the components separately at the same concentration. An effect comparable to that observed with the solid materials was found; thus, the purine bands at 1660—1700 cm.$^{-1}$ were shifted to lower frequencies, and those at 900—1100 cm.$^{-1}$ upwards, as were the bands due to the C–H deformation modes of the aromatic compounds which were not obscured by the chloroform.

By studying the effect of dilution, and using the equilibrium concentration relations, it should be possible to calculate the equilibrium constant, the degree of association in any solution, and hence the spectrum of the undissociated complex. In general, however, the spectral changes, especially in the diluted solutions, cannot be measured sufficiently accurately to afford these quantities with significance. In the case of the interaction of caffeine with 3 : 4-5 : 6-dibenzocarbazole and α-naphthol, the spectral changes were greatest and the extent of association could be approximately determined; a 0·348M-solution of caffeine and the carbazole had a degree of association of 0·44, and a 0·338M-solution of caffeine and α-naphthol one of 0·90.

As it has not been possible to obtain accurate values of the degree of association of most of the solutions and therefore of the spectral changes which would be shown by the undissociated complex, these two factors have been combined by comparing the spectral changes actually observed for various complexes at the same concentration. This has shown the associating effect of tetramethyluric acid to be greater than that of caffeine, and the effect of the aromatic compounds to be α-naphthol $\geqslant$ 3 : 4-5 : 6-dibenzocarbazole $>$ 3 : 4-benzopyrene $>$ pyrene. In approximately 0·35M-solutions, allowance being made for the two cases where precipitation occurred, the shift to lower frequencies of the purine bands at 1660—1700 cm.$^{-1}$ varied from about 12 to 3 cm.$^{-1}$, that to higher frequencies of the purine bands at 900—1100 cm.$^{-1}$ from about 6 to 2 cm.$^{-1}$ with a similar shift in the aromatic bands observable. For α-naphthol and 3 : 4-5 : 6-dibenzocarbazole, where hydrogen bonding effects are possible, part of the interaction must be of that type. The extent of hydrogen bonding, as deduced from the ratio of intensities of the associated and non-associated X–H bands, is the same in an equimolar solution of purine and aromatic compound as in a solution of the aromatic compound of the same total concentration; the associated X–H band is, however, displaced about 25 cm.$^{-1}$ less to lower frequencies, indicating a slightly weaker hydrogen bond in the complex than in the compound alone. Even where hydrogen bonding does occur, further interaction must be taking place, for certain shifts such as those in the aromatic C–H frequencies cannot be caused by that phenomenon; furthermore, in the case of pyrene and 3 : 4-benzopyrene, hydrogen bonding seems unlikely and all shifts must be due to the other type of interaction.

The ultra-violet absorption spectra also showed interaction in solution, but only in concentrated solutions. Thus, the spectra of the molecular complexes were found to be equal to the sum of the absorptions of the two components at the concentrations used for these measurements (usually approx. 4×10^{-5}M). When however the spectrum of the aromatic component was examined in the presence of a large excess of purine, a reduction in the height of the maxima and a bathochromic shift were observed (Booth and Boyland,

loc. cit.). Results and a typical example of the changes produced are shown in the Table and Fig. 2.

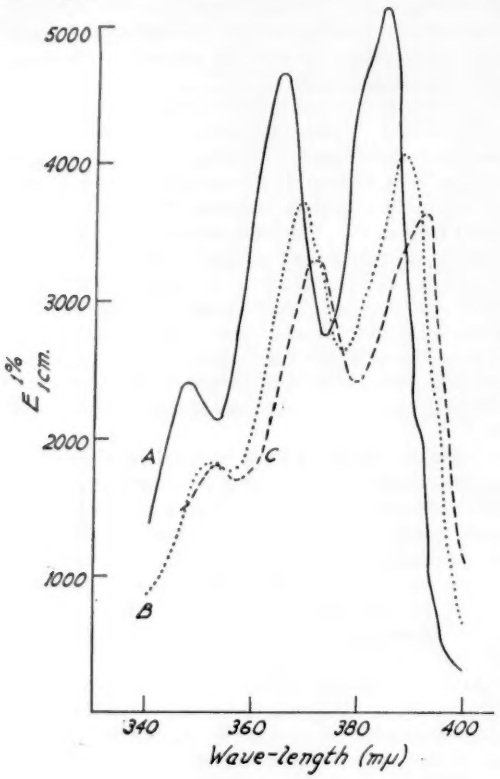


FIG. 2. *Ultra-violet absorption data.*
A, 3 : 4-*Benzopyrene in* 50% EtOH.
B, 3 : 4-*Benzopyrene in* 50% EtOH *saturated with caffeine.*
C, 3 : 4-*Benzopyrene in* 50% EtOH *saturated with tetramethyluric acid.*

Aromatic component	Concn. (mg./l.)	Solvent *	$\lambda_{max.1}$ (mμ)	Reduction in $E_{max.1}$ (%)	$\lambda_{max.2}$ (mμ)	Reduction in $E_{max.2}$ (%)
Phenanthrene	212	50% EtOH	339	—	347	—
	144	1·5% Aq. caffeine	340	33	349	32
Pyrene	3	50% EtOH	320	—	336	—
	3	1·5% Aq. caffeine	325	30	341	31
3 : 4-Benzopyrene	9	50% EtOH	365	—	384	—
	9	50% EtOH satd. with caffeine	369	21	388	21
	9	50% EtOH satd. with T.M.U.	371	29	391	29
3 : 4-5 : 6-Dibenzocarbazole	10	50% EtOH	348	—	365	—
	10	50% EtOH satd. with caffeine	350	14	367	12
	10	50% EtOH satd. with T.M.U.	350	20	367	20
3 : 4-6 : 7-Dibenzacridine	15	50% EtOH	377	—	397	—
	15	50% EtOH satd. with caffeine	379	16	400	15
	15	50% EtOH satd. with T.M.U.	380	26	401	26

* T.M.U. = tetramethyluric acid.

From both ultra-violet and infra-red spectra, therefore, an interaction between the purines and the polycyclic compounds is found to occur in concentrated solutions. Furthermore, the shifts in the infra-red spectra are the same in solution as in the solid state, and can be

correlated with specific changes in electronic distribution in the molecules. These facts all support the explanation of the formation of these complexes as due to forces of attraction between the two components arising from their mutual polarization.

This investigation has been supported by grants to the Royal Cancer Hospital and the Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

CHESTER BEATTY RESEARCH INSTITUTE, ROYAL CANCER HOSPITAL,
FULHAM ROAD, LONDON, S.W.3. [*Received, September 8th,* 1953.]

The Oxidation of Cellobiose by Periodate.

By FRANK S. H. HEAD and G. HUGHES.

[Reprint Order No. 4688.]

The oxidation of cellobiose by sodium metaperiodate has been studied. Analysis of the results suggests that the sugar is oxidised rapidly to an intermediate product with the structure of a formic ester, and that the subsequent oxidation is slow because its rate is determined by the rate of the hydrolysis of this ester. The total reaction can be represented by the equation $C_{12}H_{22}O_{11} + 11IO_4^- = 9H{\cdot}CO_2H + 2H{\cdot}CHO + CO_2 + 11IO_3^-$. The results are of significance in connection with the side reactions which occur when periodate acts on cellulose.

CONSIDERABLE interest attaches to the action of periodate on the reducing terminal glucose units in the chain-molecules of cellulose; for example, it has been suggested (Head, *J. Text. Inst.*, 1953, **44**, T209) that the "over-oxidation" that accompanies the normal Malaprade oxidation of cellulose is partly due to progressive attack on the chain-molecules from their reducing ends. It was thought that this question might be illuminated by an investigation of the action of periodate on cellobiose, the molecule of which may be regarded as a combination of the terminal glucose units of a cellulose chain-molecule.

Cellobiose was oxidised with unbuffered sodium metaperiodate in the dark at 20°. The results given in Fig. 1 show that the reaction may be divided into three main stages: (1) a rapid initial stage occupying a few hours, (2) a relatively slow second stage lasting about three weeks, and (3) an exceedingly slow final stage. During the first two stages 1 mole of cellobiose reduces about 11 moles of periodate and yields about 9 moles of formic acid, 2 moles of formaldehyde, and 1 mole of carbon dioxide. Similar figures were obtained by Courtois and Ramet (*Bull. Soc. Chim. biol.*, 1947, **29**, 240) for the oxidation of lactose and maltose by periodate at pH 1·2—2·5; they proposed the equation

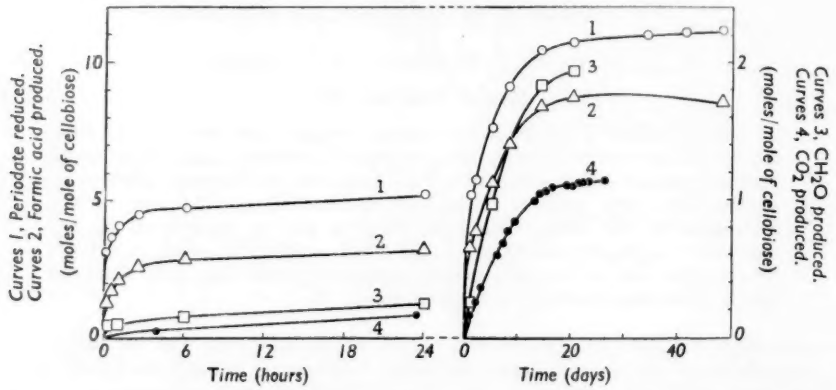
$$C_{12}H_{22}O_{11} + 11IO_4^- = 9H{\cdot}CO_2H + 2H{\cdot}CHO + CO_2 + 11IO_3^- \quad . \quad . \quad . \quad . \quad (1)$$

During the third stage formic acid and formaldehyde are very slowly oxidised to carbon dioxide (cf. Head and Hughes, *J.*, 1952, 2046). It is noteworthy that approximately 1 mole of carbon dioxide is produced before this final stage is reached.

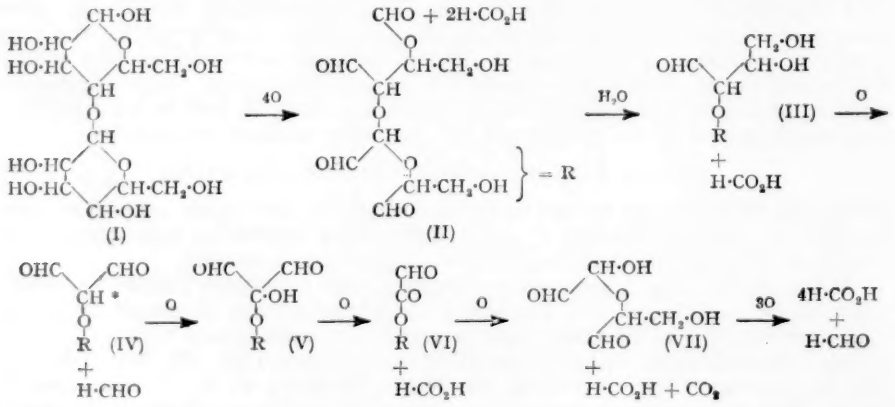
It has sometimes been supposed that under suitable conditions 1 mole of a reducing disaccharide consisting of two 1 : 4-linked hexopyranose units (I) should be oxidised quantitatively by 5 moles of periodate to 1 mole of a substance of type (IV), three of formic acid, and one of formaldehyde (Hirst *et al.*, *Nature*, 1945, **156**, 785; Potter and Hassid, *J. Amer. Chem. Soc.*, 1948, **70**, 3488). Reference to Fig. 1 shows that the composition of the system is never in agreement with exclusive oxidation to this definite stage; thus, although the reduction of 5 moles of periodate (in 18 hours) is accompanied by the formation of about 3 moles of formic acid, the formaldehyde produced amounts to only about 0·2 mole.

In Fig. 2 the yields of the various products formed during stages 1 and 2 are plotted against the amount of periodate reduced. Owing to the extreme rapidity of the initial reaction the earliest measurements of periodate consumption and yield of formic acid were made at a periodate consumption of 3·1 moles, and consequently the course of the lower part of the curve for formic acid is uncertain. Over the range covered by the observations, however, the relation between periodate consumption and yield of formic acid is virtually linear, and corresponds to a continuous production of 1 mole of formic acid per mole of periodate reduced. Extrapolation of the linear portion of the curve to the horizontal axis gives a value of almost exactly 2 moles for the periodate consumption at zero yield of formic acid, and this result suggests that the first step in the oxidation of the sugar entails the reduction of 2 moles of periodate without production of formic acid. Such a reaction

FIG. 1. *Oxidation of* 0·01M-*cellobiose with* 0·15M-*periodate in the dark at* 20°.



would correspond to the rupture of a carbon–carbon bond in each pyranose ring of the sugar molecule, but it would be less easily explicable if the reducing glucose unit reacted in the open-chain form. Moreover, oxidation of the open-chain form might be expected to produce a considerable proportion of formaldehyde from the outset, whereas the yields obtained during the early stages of the reaction are very low. It is therefore reasonable to



conclude that both halves of the cellobiose molecule react in the pyranose form. Fig. 1 shows that the rapid first stage of the reaction does not end with the rupture of a carbon–carbon bond in each glucose unit, but includes a further oxidation step. This is presumably

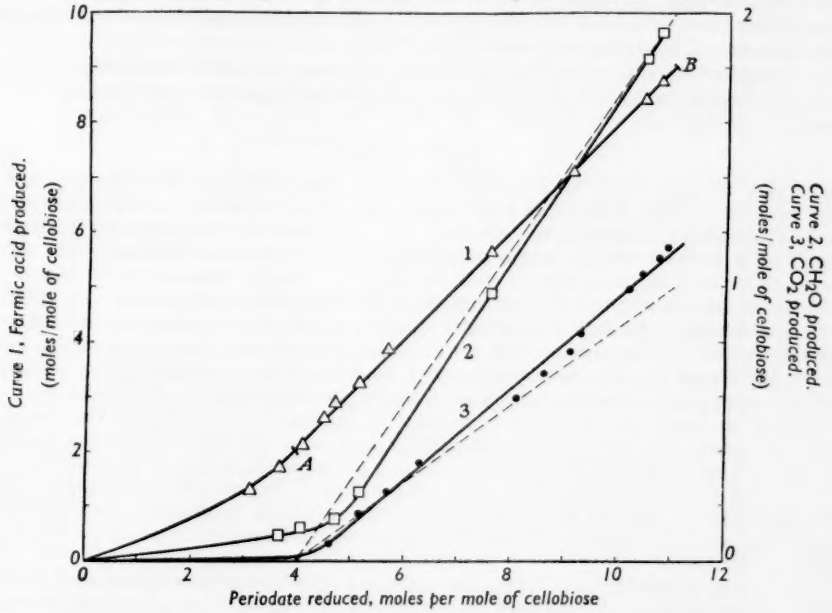
the formation of the formic ester (II), the production of which from cellobiose is represented by the equation :

$$C_{12}H_{22}O_{11} + 4IO_4^- = C_{10}H_{14}O_9 + 2H{\cdot}CO_2H + 2H_2O + 4IO_3^- \quad . \quad . \quad . \quad . \quad (2)$$

Meyer and Rathgeb (*Helv. Chim. Acta*, 1948, **31**, 1540, 1545), and Morrison, Kuyper, and Orten (*J. Amer. Chem. Soc.*, 1953, **75**, 1335), have obtained evidence of the formation of esters of this type in the periodate oxidation of lactose and maltose.

The curves for production of formaldehyde and carbon dioxide in Fig. 2 show that in stage 1 of the oxidation process the amounts of these products are very small in relation to the periodate consumption. When about 4 moles of periodate have been reduced, the slopes of the curves increase rather abruptly and then remain approximately constant as the periodate consumption increases from about 4·5 to 11 moles. The linear portions of

FIG. 2. *Oxidation of* 0·01M-*cellobiose with* 0·15M-*periodate in the dark at* 20°.



the curves correspond to zero yields of both products when about 4 moles of periodate have been reduced, *i.e.*, at the stage corresponding to quantitative formation of the ester (II).

These observations agree fairly well with what would be expected if the gross reaction in stage 2 were hydrolysis of the ester (II) and subsequent oxidation according to the equation :

$$C_{10}H_{14}O_9 + 7IO_4^- + 2H_2O = 7H{\cdot}CO_2H + 2H{\cdot}CHO + CO_2 + 7IO_3^- \quad . \quad . \quad . \quad (3)$$

The course of this reaction may be reasonably accounted for on the following basis (cf. Head, *loc. cit.*, and Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235), though other possibilities cannot be excluded. The ester (II) is probably hydrolysed, and the product (III) is then oxidised to (IV), which contains an active hydrogen atom (marked *) and should therefore be readily oxidised to (V) (cf. Sprinson and Chargaff, *J. Biol. Chem.*, 1946, **164**, 433, and Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Potter and Hassid, *loc. cit.*, pointed out that this mechanism would account for the over-oxidation of maltose). The product (V) should be oxidised first to the glyoxylic ester (VI) and then to an unstable carbonic ester which would lose carbon dioxide and give (VII) [alternatively, the same net result would follow from the hydrolysis of (VI)]. Finally,

(VII), which is a possible intermediate product in the periodate oxidation of glucose, should be oxidised to 4 moles of formic acid and one of formaldehyde.

It is probable that the production of the ester (II) from cellobiose will be rapid, but that the hydrolysis of (II) will be relatively slow. If all the subsequent reactions were instantaneous, the yields of formaldehyde and carbon dioxide, and the additional yield of formic acid, at any given degree of oxidation could be calculated by proportion from equation (3). The results corresponding to stage 2 of the oxidation process are, in general, close to the figures obtained in this manner. The calculated results for formaldehyde and carbon dioxide are represented in Fig. 2 by broken lines; the calculated line (*A*—*B*) for formic acid agrees so closely with the experimental line that the two cannot be distinguished in the Figure. The results of this comparison thus support the view that the hydrolysis of (II) is the rate-controlling process and that the subsequent oxidation processes are, as a whole, much faster. The small but appreciable yields of formaldehyde before the end of stage 1 suggest that, as might be expected, some of the cellobiose is completely oxidised before all has been converted into the ester (II). The yield of carbon dioxide at this stage is less than would be expected, however.

The complete oxidation of cellobiose to simple products makes it seem probable that the effect of periodate on cellulose will include a step-wise degradation proceeding from the terminal reducing units.

Experimental

Reaction mixtures were kept in the dark in a thermostat at 20°. Formic acid was determined by titration with alkali after destruction of the excess of periodate with ethylene glycol and aeration to remove carbon dioxide. Formaldehyde was determined by the dimedone method after removal of the excess of periodate and iodate with arsenite. The detailed procedures for both methods were as given by Head and Hughes (*loc. cit.*).

Periodate was determined by the convenient Müller–Friedberger method (*Ber.*, 1902, **35**, 2652), in which the periodate is reduced with iodide in weakly alkaline solution and the liberated iodine is titrated with arsenite. This method was selected with due regard to the work of Hughes and Nevell (*Trans. Faraday Soc.*, 1948, **44**, 941) on the determination of periodate in the presence of partially oxidised glucose. Their results show that the Fleury–Lange method of analysis, in which the periodate is reduced by an excess of arsenite in the presence of potassium iodide and sodium hydrogen carbonate, is unsatisfactory under these conditions, but that reliable results are obtained by reduction of the oxidant with iodide in acid solution and titration of the liberated iodine with thiosulphate. Preliminary tests showed that the Müller–Friedberger method is unsatisfactory with solutions containing partially oxidised glucose, but gives the same result as the thiosulphate method with solutions containing partially oxidised cellobiose.

The carbon dioxide formed during the oxidation of cellobiose was determined as follows. A slow stream of nitrogen, freed from carbon dioxide, was passed through a periodate solution until the issuing gas was free from carbon dioxide. A weighed amount of cellobiose was then added to the solution, and the gas, after being dried with phosphoric oxide, was passed through a weighing tube containing "Carbosorb" backed with phosphoric oxide. A preliminary experiment showed that the tube did not increase in weight during 2 hr. when the reaction mixture was replaced by 0·2N-formic acid solution.

The British Cotton Industry Research Association,
Shirley Institute, Didsbury, Manchester.

[*Received, September 29th*, 1953.]

Alkenylation employing Lithium Alkenyls. Part VIII. Studies on Alkadienyl Derivatives.*

By E. A. Braude and E. A. Evans.

[Reprint Order No. 4745.]

The scope of the method of direct alkenylation with lithium alkenyls has been extended by demonstrating the formation of alkadienyl derivatives.

*iso*Phorone is converted by phosphorus pentachloride into, mainly, the chloro*cyclo*hexadiene (IV), formerly regarded as (II), and the phosphonic acid (V). Metallation of the chloro-diene with lithium, followed by carboxylation, gives the two 3 : 5 : 5-trimethyl*cyclo*hexadienecarboxylic acids (VI) and (VII), the structures of which are established spectroscopically and by hydrogenation.

Chloro*cyclo*heptadiene, similarly prepared from *cyclo*heptenone, is unreactive towards lithium, in contrast to 1-chloro*cyclo*heptene. The acyclic chloro-diene (XVI), derived from mesityl oxide, undergoes metallation and carboxylation, but instead of the expected diene-acid (XVII), a cyclic dimeric product regarded as (XIX) and formed by Diels–Alder addition with the starting chloride, is obtained.

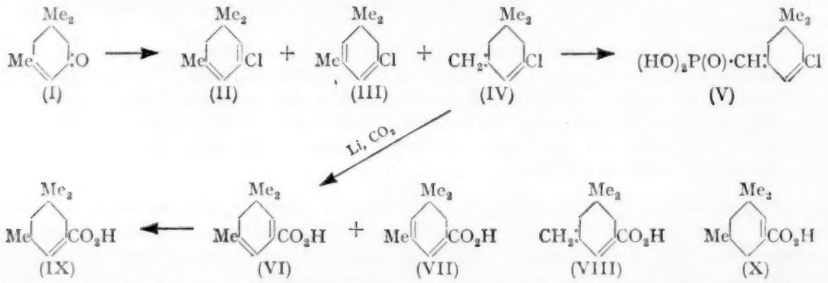
It has been shown in previous papers that lithium alkenyls can be obtained from a considerable range of alkylated vinyl halides and will undergo many useful reactions. This paper describes an extension of this approach to another type of substituted vinyl halide, namely, alkadienyl-lithium derivatives containing lithium directly attached to a conjugated diene system.

With the expectation (subsequently confirmed) that a cyclic alkadienyl-lithium derivative would have a better chance of survival for a useful life-time than an acyclic one, we selected the readily available *iso*phorone (I) for a first investigation. The conversion, by means of phosphorus pentachloride in chloroform, of *iso*phorone into a chloro-diene formulated as (II) was described by Knoevenagel and Fischer (*Annalen*, 1897, **297**, 191). When 1 molar proportion of phosphorus pentachloride is used, the yields obtained under these conditions are very low and much unchanged ketone is recovered, but somewhat better yields (up to 30%) can be attained in the absence of solvent. The chloro-diene obtained in this way boils over a very narrow range, but shows three distinct ultra-violet absorption maxima, at 2370, 2680, and 2780 Å, which are of varying relative intensity and almost certainly belong to three separate species.† The location of the 2680 Å band is that expected for the direct reaction product (II), formed by addition of phosphorus pentachloride to the carbonyl group followed by 1 : 2 elimination of $HO{\cdot}PCl_4$ (cf. Braude and Forbes, *J.*, 1951, 1755); the wave-length displacement with respect to *cyclo*hexa-1 : 3-diene ($\lambda_{max.}$ 2560 Å) corresponds almost exactly to the sum of the bathochromic effects of an α-methyl substituent ($+\Delta\lambda$ 70 Å) and β-chloro-substituent ($+\Delta\lambda$ 60 Å) in a diene system (Bowden, Braude, and Jones, *J.*, 1946, 948). The location of the 2780 Å band is that expected for the isomer (III), the slightly greater wave-length displacement with respect to *cyclo*hexa-1 : 3-diene being due to the relatively larger bathochromic effect of a chloro-substituent attached to the terminal position of the diene system.† Lastly, the 2370 Å band must belong to the isomer (IV) containing one exocyclic double bond, the wave-length displacement with respect to 3-methylene*cyclo*hexene (2280 Å; Braude and Wheeler, unpublished work; cf. β-phellandrene, $\lambda_{max.}$ 2320, Macbeth, Smith, and West, *J.*, 1938, 119) again being due the terminal chloro-substituent. The intensity of the 2370 Å band in the chloro-diene mixture is always much higher ($\varepsilon \sim 9000$) than that of the other two bands which are of similar intensity ($\varepsilon \sim 2000$); assuming the extinction coefficients of the pure compounds to be in the same ratio as those of 3-methylene*cyclo*hexene (ε 10,000) and *cyclo*hexa-1 : 3-diene (ε 8000) gives the average proportions of (II),

* Part VII, *J.*, 1952, 1425.

† The possibility that the 2680 and 2780 Å bands belong to one species, (II) or (III), cannot be excluded.

(III), and (IV) in the crude reaction product as *ca.* 1 : 1 : 8. The three chloro-dienes may be regarded as derived from the three possible enols of *iso*phorone, although (III) and (IV) may actually be formed from (II) by prototropic double-bond migration. On treatment with Brady's reagent, the chloro-diene mixture gave *iso*phorone 2 : 4-dinitrophenylhydrazone, though only in 30% yield. Treatment with aqueous silver nitrate also gave *iso*phorone, whereas with ethanolic silver nitrate a ketone was obtained which had physical properties identical with those of *iso*phorone but formed a 2 : 4-dinitrophenylhydrazone of much lower m. p. This may be an isomeric derivative of *iso*phorone, as observed in other cases (cf. Dirscherl and Nahm, *Ber.*, 1940, **73**, 448; Theilacker, *ibid.*, 1949, **82**, 190; Braddock and Willard, *J. Amer. Chem. Soc.*, 1951, **73**, 5866); alternatively, it may be the derivative of 2 : 4 : 4-trimethyl*cyclo*hex-2-enone produced by reverse hydration of the vinyl chloride grouping.



In addition to the chloro-dienes, the reaction of *iso*phorone with phosphorus pentachloride (1 mol.) affords a small amount of a solid, m. p. 139°, $C_9H_{14}O_3ClP$. When, in an attempt to improve the yields of chloro-dienes, the reaction was carried out with 2 molar proportions of phosphorus pentachloride, this solid was the main product. It proved to be a dibasic phosphonic acid and its spectral properties indicate that it has the structure (V) and is formed by the addition of phosphorus pentachloride to the exocyclic double bond in (IV), followed by hydrolysis (cf. Kosolapoff, " Organic Reactions," Vol. VI, 1951, p. 291). The high intensity of the ultra-violet absorption ($\lambda_{max.}$ 2510 Å; ε 28,000) shows that the one double bond is exocyclic while the bathochromic displacement with respect to (IV) is ascribable to the auxochromic effect of the conjugated phosphorus-containing group (cf. Bowden and Braude, *J.*, 1952, 1068); the infra-red spectrum exhibits bands at 1614 and 1573 cm.$^{-1}$ associated with C=C stretching vibrations, and 1022 and 960 cm.$^{-1}$ associated with $-PO(OH)_2$ bending vibrations (cf. Halman and Pinchas, *J.*, 1953, 627; Bellamy and Beecher, *ibid.*, p. 729).

The chloro-dienes are rather unstable compounds and difficult to separate, but the predominating isomer (IV) was obtained nearly pure by fractionation on a small scale. The freshly distilled material reacted fairly readily with almost the theoretical amount of lithium in boiling ether, and on carboxylation furnished a solid acid in up to 15% yield. The conditions of formation of the lithium alkadienyl are considerably more critical than those of similar lithium alkenyls (*e.g.*, *cyclo*hexenyl-lithium; Braude and Coles, *J.*, 1950, 2014); and the alkadienyl derivative is evidently rather unstable, for, if the optimum reaction period was doubled, the yield of acid obtained on carboxylation dropped to 0·5%. The acid, which was also rather unstable, analysed correctly for the expected product (VIII) and had a sharp melting point when freshly purified by vacuum-sublimation or crystallisation, but showed two distinct ultra-violet absorption bands, at 2640 and 2910 Å, in solution. The sum of the intensities of the two bands was approximately constant in different solvents, but the relative intensities depended on the pH (see Table), and the two bands clearly belong to two isomeric species in equilibrium. The location of the 2640 Å band is compatible with structure (VIII) but its low intensity would correspond to the presence of less than 20% of this isomer (cf. sorbic acid which has $\lambda_{max.}$ 2580 Å, ε 25,000, in ethanol). Moreover, the infra-red spectrum of the diene-acid fails to show the C–H bending frequency at 890 cm.$^{-1}$ characteristic of a $CH_2{=}C<$ grouping. The

2640 Å band is therefore attributed to structure (VI) containing the " cross-conjugated " *cyclo*hexa-1 : 5-dienecarboxylic acid system which would be expected to exhibit a maximum in this region, although no other examples appear to be known. The 2910 Å band, on the other hand, is attributed to structure (VII) containing the terminally conjugated *cyclo*hexa-1 : 3-dienecarboxylic acid system.

Ultra-violet light absorption of trimethylcyclohexadienecarboxylic acids (VI) ⇌ (VII), *their salts, and their methyl esters.*

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\varepsilon_{2640} + \varepsilon_{2910}$
Acids : in hexane	2640	5200	2910	4800	10,000
,, dioxan	2640	5200	2910	4900	10,100
,, ethanol	2640	5300	2910	4700	10,000
Salts : in ethanol–0·1M-KOH	2610	6000	2910	3800	9,800
Esters : in ethanol	2640	5900	2920	5000	10,900
,, ethanol–0·1M-KOH	2640	5900	2920	5000	10,900

The formation of lithium alkenyls is not normally accompanied by double-bond migration (cf. Braude and Timmons, *J.*, 1950, 2000; Braude and Coles, *J.*, 1950, 2014; 1951, 2078) and it seems probable that the rearrangement of the exocyclic system present in the chloride (IV) to the *cyclo*hexadiene system present in the acids (VI) and (VII) occurs during, rather than before, the carboxylation of the alkadienyl-lithium derivative when the lithium salt of the acid (VIII) is formed. The prototropic mobility of the ethylenic acids and their salts is well known and the exocyclic double-bond arrangement in (VIII) would be expected to be less stable than the more highly hyperconjugated cyclic double-bond arrangements in (VI) and (VII) which should be almost equally stable. The two *cyclo*hexadiene derivatives thus co-exist in about equal proportions, though the exact equilibrium point differs in the acids and their salts, as in other cases (cf. Linstead and Noble, *J.*, 1934, 614, and earlier papers). The predominance of the exocyclic isomer (IV) in the corresponding chlorides may be due to the smaller importance of hyperconjugation in the absence of a carboxyl group, or, more probably, to the fact that the method of preparation does not result in an equilibrium mixture in this case.

Treatment of the mixture of acids (VI) and (VII) with diazomethane in ether gave a mixture of the corresponding methyl esters which showed very similar spectral properties in the ultra-violet (see Table) and infra-red (see Experimental section) and were also inseparable by small-scale fractionation. Neither the esters nor the acids furnished maleic anhydride adducts under the usual conditions. On hydrogenation over platinum oxide in ethyl acetate, the diene-acids gave a monoene-acid which exhibited a maximum at 2170 Å (ε 9500) and therefore contained the double bond in conjugation with the carboxyl group (cf. *cyclo*hex-1-enecarboxylic acid, $\lambda_{max.}$ 2120 Å, ε 11,000; Braude and Coles, *loc. cit.*). This acid is regarded as (IX), produced by 1 : 4-addition of hydrogen to the *cyclo*hexadiene system in (VI) and 1 : 2-addition in (VII), although the alternative structure (X) is not excluded. Hydrogenation of the diene acids over platinum oxide in acetic acid resulted in the uptake of two mols. of hydrogen and gave 3 : 3 : 5-trimethyl*cyclo*hexanecarboxylic acid. An authentic specimen of the latter was prepared from dihydro*iso*phorone by reduction to the alcohol, conversion into the bromide, and carboxylation of the Grignard derivative.

The highest yields of acids obtained from the lithium derivative of (IV) compare favourably with those obtained in similar carboxylations (cf. Braude and Timmons, and Braude and Coles, *locc. cit.*), but none of the corresponding dialkenyl ketone which normally forms the major product could be isolated in the present case. A small quantity of a high-melting ketone $C_{18}H_{30}O_2$ was separated from the neutral fraction, but was not further investigated. No pure products are isolated from the reaction of the alkadienyl-lithium with acetaldehyde, benzaldehyde, or benzophenone, which usually give the expected alcohols in good yields. As has been indicated, even the trimethyl*cyclo*hexadienyl chlorides and carboxylic acids are unstable and the failure to isolate other types of derivatives is undoubtedly due to the high reactivity and ease of isomerisation of this system.

Even greater instability is to be expected for unsubstituted *cyclo*hexadienyl derivatives,

but it was hoped that some of the complications just described would be absent in the *cyclo*heptadiene system which is also of particular interest for synthetic purposes (cf. Braude and Forbes, *J.*, 1953, 2208). *cyclo*Hept-2-enone (XI) which has not been previously described although it has been mentioned in the literature (cf. Kötz, *Annalen*, 1913, **400**, 80; Dauben and Ringold, *J. Amer. Chem. Soc.*, 1951, **73**, 876) was prepared by bromination of *cyclo*heptanone with bromine in chloroform in the presence of calcium carbonate, followed by dehydrobromination with collidine at 180°. Even when a deficiency of bromine was used, some dibromo-ketone was produced in the first step and it was necessary to separate the mixture of unchanged *cyclo*heptanone, 1-bromo*cyclo*heptanone, and dibromo-ketone by careful fractionation. Alternatively, chloro*cyclo*heptanone (Kötz, *Annalen*, 1913, **400**, 53) may be employed as intermediate; the monochlorination proceeded in better yield than bromination, but the dehydrochlorination required a higher temperature (cf. Warnhoff and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 494) and the overall yield was somewhat lower. The *cyclo*heptanone obtained by either procedure exhibited an absorption band at 2270 Å as expected for (XI), and its skeletal structure was confirmed by catalytic hydrogenation to *cyclo*heptanone. However, the intensity of absorption of the unsaturated ketone was only about half the usual value and the crude semicarbazone showed two bands, one at 2650 Å corresponding to the derivative of an αβ-ethylenic ketone (cf. Evans and Gillam, *J.*, 1943, 565), and another at 2270 Å, corresponding to the derivative of an unconjugated ketone (Braude and Timmons, *J.*, 1953, 3131). *cyclo*Heptenone prepared by this method is thus evidently a mixture of the αβ- (XI) and the βγ-ethylenic isomer (XII), as observed in other cases (cf. Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890, and references there cited). The two isomers could not be separated by small-scale fractionation, and crystallisation of the mixture of semicarbazones gave only the higher-melting derivative of (XII) in a state of purity; on the other hand, treatment with Brady's reagent gave a chromatographically homogeneous 2 : 4-dinitrophenylhydrazone, the light absorption of which ($\lambda_{max.}$ 3770 Å) indicates that it is the derivative of (XI) (cf. Braude and Jones, *J.*, 1945, 498). With phosphorus pentachloride, *cyclo*heptenone was converted into a mixture of the required chloro*cyclo*hepta-1 : 3-diene (XIII) or (XIV) and 3 : 3-dichloro*cyclo*heptene.

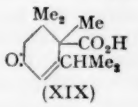
(XI) (XII) (XIII) (XIV)

Treatment of the dichloride with ethanolic potassium hydroxide gave the chlorodiene; its ultra-violet light absorption ($\lambda_{max.}$ 2510 Å) shows the expected small bathochromic shift with respect to *cyclo*heptadiene ($\lambda_{max.}$ 2480 Å; Pesch and Friess, *J. Amer. Chem. Soc.*, 1950, **72**, 5756), similar to that found in the *cyclo*hexadiene system, but does not distinguish reliably between structures (XIII) and (XIV). The chloro*cyclo*heptadiene proved extremely unreactive towards lithium; only a fraction of the stoicheiometric proportion of metal was consumed and on carboxylation only traces of non-crystalline acidic products were obtained. This lack of reactivity is somewhat surprising since 1-chloro*cyclo*hexene (Braude and Coles, *loc. cit.*) and 1-chloro*cyclo*heptene (Braude, Forbes, and Evans, *J.*, 1953, 2202) are metallated with comparable ease. It is possible that double-bond isomerism in the chloro*cyclo*heptadiene is responsible; the ease of direct metallation reactions is known to be highly sensitive to the homogeneity of the organic halide (cf. Part I, *J.*, 1950, 2000).

Despite this discouraging result, the metallation of an acyclic chloro-diene was next attempted. A suitable example appeared to be 2-chloro-4-methylpenta-1 : 3-diene (XVI) obtainable from mesityl oxide and phosphorus pentachloride (Baeyer, *Annalen*, 1866, **140**, 298). This chloro-diene reacted quite readily with lithium but on carboxylation did not give the expected diene-acid (XVII). Instead, an acid $C_{13}H_{20}O_3$ was obtained, the spectral properties ($\lambda_{max.}$ 2430 A, ε 10,000; $\nu_{max.}$ 1654, 1580 cm.$^{-1}$) of which indicated the presence of the carboxyl group but also of a keto-group conjugated with *one* ethylenic double bond;

this, together with the high melting point (187°) leads to the conclusion that the acid contains one alicyclic ring. The molecular formula corresponds to an adduct of the expected diene-acid (XVII; $C_7H_{10}O_2$) and one molecule of mesityl oxide (XV; $C_6H_{10}O$), which would be the hydrolysis product of the starting chloride (XVI). The most probable structure of the keto-acid is (XIX), formed by Diels–Alder addition of the lithium salt of the diene-acid in its isomeric form (XVIII) to the starting chloride, followed by prototropic shift of the double bond into the ring and hydrolysis of the vinyl chloride grouping during the working-up. The occurrence of this type of side-reaction severely restricts the potential synthetic usefulness of acyclic alkadienyl-lithium derivatives and, not unexpectedly, no pure products could be isolated from the reactions with other carbonyl compounds, such as formaldehyde and benzophenone.

$CMe_2{:}CH{\cdot}COMe \longrightarrow CMe_2{:}CH{\cdot}CCl{:}CH_2 \longrightarrow CMe_2{:}CH{\cdot}C(CO_2H){:}CH_2$
(XV) (XVI) (XVII)

$\longrightarrow CO_2H{\cdot}CMe{:}CH{\cdot}CMe{:}CH_2 \longrightarrow$ 
(XVIII) (XIX)

Experimental

M. p.s were taken on a Kofler block and are corrected.

Analytical data were determined by Mr. F. H. Oliver and the staff of the microanalytical laboratory of this Department. Ultra-violet light absorptions were determined by Mrs. A. I. Boston using Hilger–Spekker and Unicam S.P. 500 instruments. Infra-red spectra were kindly determined by Dr. E. S. Waight, using a single-beam Grubb–Parsons instrument. The intensities of infra-red absorption bands are indicated qualitatively by vs (very strong), s (strong), or m (medium).

1-*Chloro*-5 : 5-*dimethyl*-3-*methylene*cyclo*hexene* (IV).—*iso*Phorone (200 g.) was added slowly to phosphorus pentachloride (300 g.) with rapid stirring and external cooling. Stirring was continued overnight, and the mixture was then added to ice-water (2 l.) and extracted with ether (1 l.). The ethereal extract was dried (Na_2SO_4) and the solvent removed under reduced pressure. On cooling to 0°, a solid (9·8 g.) separated which was filtered off and after recrystallisation from ethyl acetate had m. p. 138—139°, undepressed on admixture with the phosphonic acid (V) described below.

The liquid product was fractionated through an 8″ Dufton column, giving a mixture of 1-chloro-5 : 5-dimethyl-3-methylene*cyclo*hexene, and 3-chloro-1 : 5 : 5- and 1-chloro-3 : 5 : 5-trimethyl*cyclo*hexa-1 : 3-diene (58 g., 26%), b. p. 65—66°/17 mm., n_D^{21} 1·4910—1·4920 (Found : C, 69·2; H, 8·4; Cl, 22·4. Calc. for $C_9H_{13}Cl$: C, 69·0; H, 8·3; Cl, 22·7%). Light absorption in hexane : $\lambda_{max.}$ 2360, 2680, and 2780 Å; ε 9000, 2000, and 1500 respectively. The yield quoted is the best obtained; in other runs it ranged from 8 to 26%, the average yield in 8 runs being 16%. When the reaction was carried out in chloroform solution the yield was reduced (cf. Knoevenagel and Fischer, *Annalen*, 1897, **297**, 191). The composition of the chloro-diene mixture as indicated by the intensities of the three ultra-violet absorption bands also showed some variation.

Higher-boiling fractions consisted of mixtures of the chloro-diene, unchanged *iso*phorone, and 1 : 1-dichloro-3 : 3 : 5-trimethyl*cyclo*hexane.

Refractionation of the above chloro-diene mixture gave 1-*chloro*-5 : 5-*dimethyl*-3-*methylene*-cyclo*hexene*, b. p. 70°/16 mm., n_D^{19} 1·4921, $\lambda_{max.}$ 2360, ε 10,500 in hexane (Found : Cl, 22·2%).

Hydrolysis of 1-*Chloro*-5 : 5-*dimethyl*-3-*methylene*cyclo*hexene*.—(*a*) The chloro-diene (1 g.) was refluxed with 2 : 4-dinitrophenylhydrazine (1 g.) and sulphuric acid (3 g.) in methanol (15 ml.) and water (5 ml.) for 30 min. On cooling, *iso*phorone 2 : 4-dinitrophenylhydrazone (0·5 g.) separated which after one crystallisation from ethyl acetate had m. p. and mixed m. p 146°.

(*b*) The chloro-diene (1·2 g.) was refluxed with silver nitrate (3 g.), water (50 ml.), and 1 drop of sulphuric acid for 3 hr. The silver chloride (0·25 g., 7%) was filtered off and the solution extracted with ether, giving *iso*phorone, identified as in (*a*).

(*c*) The chloro-diene (3 g.) was refluxed with silver nitrate (4 g.) in ethanol (30 ml.) containing 1 drop of nitric acid for 1 hr. Water was added and the precipitate of silver chloride

(0·9 g., 7%) filtered off. Extraction of the filtrate with ether and fractionation gave a ketone (1·2 g.), b. p. 93—94°/17 mm., n_D^{22} 1·4855, $\lambda_{max.}$ 2340 Å, ε 11,700 in EtOH. It formed a 2 : 4-*dinitrophenylhydrazone* which crystallised from ethyl acetate in plates, m. p. 124°, and had $\lambda_{max.}$ 3900 Å, ε 28,600 in EtOH (Found: C, 57·0; H, 6·0; N, 17·3. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%). This is presumably an isomer of *iso*phorone 2 : 4-dinitrophenylhydrazone or the derivative of 2 : 4 : 4-trimethyl*cyclo*hex-2-enone.

3-*Chloro*-5 : 5-*dimethyl*cyclo*hex*-2-*enylidenemethylphosphonic Acid* (V).—*iso*Phorone (28 g.) was caused to react with phosphorus pentachloride (78 g.), and the products were worked up as above. After the removal of ether, solid material (15 g.) separated and was filtered off. Crystallisation from ethyl acetate gave the *phosphonic acid*, m. p. 139° (Found: C, 45·6; H, 6·2; P, 12·7; Cl, 15·1. $C_9H_{14}O_3PCl$ requires C, 45·7; H, 6·0; P, 13·1; Cl, 15·0%). A solution in aqueous ethanol was acid to litmus and liberated carbon dioxide from sodium carbonate. The equivalent weight, kindly determined alkalimetrically by Dr. H. Coates (Albright and Wilson, Ltd.), was 118 (Calc.: 118) and no orthophosphoric acid was produced on fusion with potassium hydroxide; hence the acid is a dibasic phosphonic acid and not a phosphoric acid monoester. Ultra-violet light absorption: $\lambda_{max.}$ 2510 and 2560 Å (ε 28,300) in EtOH. Infra-red light absorption: $\nu_{max.}$ 1614 (m), 1573 (m), 1022 (s), and 960 (s) cm.$^{-1}$ (Nujol mull).

3 : 3 : 5-*Trimethyl*cyclo*hexa*-1 : 5- (VI) *and* 3 : 5 : 5-*Trimethyl*cyclo*hexa*-1 : 3-*dienecarboxylic Acid* (VII).—Freshly distilled 1-chloro-5 : 5-dimethyl-3-methylene*cyclo*hexene (50 g.) in anhydrous ether (100 ml.) was added to a vigorously stirred, finely divided suspension of lithium (13·1 g.) in ether (1 l.) under nitrogen. After about 20 min. the solution became cloudy and was then heated to gentle reflux. Heating was continued for 15 hr. during which the mixture first became red, then brown and finally orange; these characteristic colour changes are different from those observed with monoethylenic lithium alkenyls (cf. Braude and Coles, *J.*, 1950, 2014; Braude and Forbes, *J.*, 1951, 1755). The solution of alkadienyl-lithium was filtered under nitrogen through glass wool into a flask containing excess of solid carbon dioxide (1500 g.). The amount of unchanged lithium recovered from the residue was 9·4 g.; the amount consumed was therefore 3·7 g., or 82% based on the chloro-diene. After the filtrate had attained room temperature, N-hydrochloric acid (500 ml.) was added, the ethereal layer was separated, and the aqueous layer extracted with ether. The combined ethereal extracts were shaken with saturated aqueous sodium carbonate (3 × 100 ml.), and the ethereal (A) and the aqueous layer (B) were separated.

The ethereal layer was concentrated under reduced pressure and, on being kept, deposited a crystalline *ketone* (0·5 g.) which after sublimation at 160°/10^{-5} mm. had m. p. 166°, $\lambda_{max.}$ 2850 Å, $E^{1\%}_{1\,cm.}$ 2·4 in EtOH (Found: C, 77·6; H, 10·9. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8%). Treatment with Brady's reagent gave a 2 : 4-*dinitrophenylhydrazone* which was crystallised from ethyl acetate and had m. p. 261—262° (decomp.), $\lambda_{max.}$ 3680 Å, $E^{1\%}_{1\,cm.}$ 700 in $CHCl_3$ (Found: C, 54·3; H, 6·5; N, 15·6%).

Acidification of the aqueous layer (B) with hydrochloric acid precipitated a brown gum which was extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated, and the residue (10 g.) was slowly sublimed in a short-path sublimation apparatus at 80°/10^{-5} mm., giving a mixture of the diene-acids (7·4 g., 14%), m. p. 88° (Found: C, 72·1; H, 8·5. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·5%). Ultra-violet light absorption: see Table. Infra-red light absorption (Nujol mull): $\nu_{max.}$ 1682 (s; C=O stretching), 1646 and 1575 cm.$^{-1}$ (m; C=C stretching).

The above conditions of metallation are those which gave the highest yields of diene-acids. The results of other typical runs are tabulated below.

Li used (atom proportions)	5·8	4·6	2·4	2·7
Li consumed (atom proportions)	1·6	2·0	1·4	1·1
Reaction time (hr.)	15	15	15	36
Yield of acids (%)	14	5	5	0·5

Esterification of Diene-acids.—Treatment of the acids (0·9 g.) with excess of diazomethane in ether afforded the methyl esters (1·0 g.), b. p. 53°/0·5 mm., n_D^{23} 1·4934 (Found: C, 73·1; H, 9·0. Calc. for $C_{11}H_{16}O_2$: C, 73·3; H, 8·95%). Ultra-violet light absorption: see Table. Infra-red light absorption (liquid film): $\nu_{max.}$ 1740 (vs; C=O stretching), 1652, 1626, 1606, 1585 (m; C=C stretching), 1266, 1240, 1198 (s; C–O stretching), 1078 (s), and 824, 804 cm.$^{-1}$ (m; CR_2=CR–H bending).

Hydrogenation of Diene-acids.—(*a*) Hydrogenation of the above diene-acids (0·5 g.) in methanol (15 ml.) in the presence of platinum oxide resulted in the uptake of 65 ml. of hydrogen during 4 hr. (at 20°/760 mm. Calc. for 1 mol., 72 ml.), giving 3 : 3 : 5-*trimethyl*cyclo*hex*-1-*ene*-

carboxylic acid (0·3 g.), m. p. 65° (Found: C, 71·0; H, 9·7. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). Light absorption in EtOH: $\lambda_{max.}$ 2170 Å, ε 9200.

(*b*) Hydrogenation of the diene-acids (0·3 g.) in glacial acetic acid (25 ml.) in the presence of platinum oxide resulted in the uptake of 87 ml. of hydrogen (at 20°/761 mm. Calc. for 2 mols., 87 ml.). There was a marked decrease in the rate of uptake after 1 mol. had been absorbed. Dilution with water and extraction with ether gave an oil which was treated with thionyl chloride followed by aniline, to give 0·2 g. of 3 : 3 : 5-trimethyl*cyclo*hexylacetanilide, m. p. 115—116°, undepressed on admixture with the authentic specimen described below.

3 : 3 : 5-*Trimethyl*cyclo*hexanecarboxylic Acid*.—*iso*Phorone (100 g.) in ethyl acetate (200 g.) was hydrogenated over platinic oxide, to give 3 : 3 : 5-trimethyl*cyclo*hexanone (90 g., 89%), b. p. 68°/15 mm., n_D^{16} 1·4492 (cf. Skita, *Ber.*, 1909, **42**, 1630). The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol in plates, m. p. 115—116° (Found: C, 56·0; H, 6·4; N, 17·3. $C_{15}H_{20}O_4N_4$ requires C, 56·2; H, 6·3; N, 17·5%). (Morgan and Hardy, *Chem. and Ind.*, 1933, 518, give m. p. 145—147°, presumably due to an isomer; alternatively, it seems possible that their derivative was, in fact, that of *iso*phorone and not of dihydro*iso*phorone.)

The ketone (30 g.) was reduced with lithium aluminium hydride (7 g.) in ether (350 ml.) at 0°, and then at 20°, to 3 : 3 : 5-trimethyl*cyclo*hexanol (26 g., 85%), b. p. 83°/10 mm., n_D^{20} 1·4558. Knoevenagel, *loc. cit.*, gives b. p. 92°/12 mm., n_D^{16} 1·4550, for the *cis*-isomer; this stereochemical assignment is now confirmed, since reduction by lithium aluminium hydride will give the thermodynamically more stable *cis*-isomer (cf. Barton, *J.*, 1953, 1027) with both the 1-hydroxyl and the 3-methyl group equatorial. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 71° (Found: C, 57·5; H, 6·1; N, 8·6. $C_{16}H_{20}O_6N_2$ requires C, 57·2; H, 6·0; N, 8·3%).

A mixture of the alcohol (21·2 g.) and phosphorus tribromide (40·6 g.) was kept overnight at 20° and then refluxed for 3 hr. After this had cooled, water (100 ml.) was added and the product extracted with ether. Fractionation gave 3-bromo-1 : 1 : 5-trimethyl*cyclo*hexane (14 g., 46%), b. p. 79°/10 mm., n_D^{22} 1·4823 (Found: C, 52·8; H, 8·3; Br, 39·4. $C_9H_{17}Br$ requires C, 52·7; H, 8·3; Br, 39·0%).

A solution of the foregoing bromide (7·65 g.) in ether (80 ml.) was stirred and refluxed with magnesium (0·95 g.) and a trace of iodine and methyl iodide. Reaction set in after about 1 hr. and was complete after 3 hr. Excess of solid carbon dioxide (50 g.) was added, then, after 2 hr., 2N-sulphuric acid (50 ml.), and the ethereal layer was separated and extracted with aqueous sodium carbonate. The alkaline extract was acidified with hydrochloric acid and extracted with ether. This ethereal extract was dried (Na_2SO_4) and distilled, giving 3 : 3 : 5-*trimethyl*-cyclo*hexanecarboxylic acid* (1·9 g., 30%), m. p. 43°, b. p. 90°/0·5 mm., n_D^{24} 1·4571 (Found: C, 70·5; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%). The *methyl ester*, prepared in quantitative yield by treatment with excess of diazomethane in ether, had b. p. 46°/0·5 mm., n_D^{25} 1·4452 (Found: C, 72·0; H, 11·1. $C_{11}H_{20}O_2$ requires C, 71·7; H, 10·9%). The *anilide*, prepared *via* the acid chloride as above, crystallised from aqueous methanol in plates, m. p. 118—119° (Found: N, 5·8. $C_{16}H_{23}ON$ requires N, 5·7%).

2-*Bromo*cyclo*heptanone*.—Bromine (240 g.) in chloroform (150 ml.) was added during 2 hr. to a stirred mixture of *cyclo*heptanone (168 g.), chloroform (100 ml.), water (300 ml.), and calcium carbonate (75 g.). The flask was initially warmed to start the reaction and later cooled when necessary. Stirring was continued for 5 hr. after all the bromine had been added and the mixture was then extraced with ether (2 × 250 ml.). The ethereal extract was washed with water, dried (Na_2SO_4), and fractionated, giving (i) a mixture of unchanged *cyclo*heptanone and 2-bromo*cyclo*heptanone (55 g.), b. p. 60—78°/2 mm., n_D^{23} 1·4665—1·4800, (ii) 2-bromo*cyclo*-heptanone (75 g., 28%), b. p. 80—84°/2 mm., n_D^{23} 1·5100, (iii) dibromo*cyclo*heptanone (3 g.), b. p. 94—98°/1 mm., n_D^{23} 1·5385, and higher-boiling residues. Redistillation of fraction (ii) gave pure 2-*bromo*cyclo*heptanone*, b. p. 105°/10 mm., n_D^{22} 1·5137 (Found: C, 44·5; H, 6·0; Br, 41·5. $C_7H_{11}OBr$ requires C, 44·0; H, 5·8; Br, 41·8%). On treatment with 2 : 4-dinitrophenylhydrazine in methanol–sulphuric acid it gave 2-*methoxy*cyclo*heptanone* 2 : 4-*dinitrophenylhydrazone* which after chromatography on alumina in benzene–chloroform crystallised from ethyl acetate–methanol in yellow needles, m. p. 109° (Found: C, 52·4; H, 6·0; N, 17·5. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%). [Since the present work was done, the preparation of 2-bromo*cyclo*heptanone in unstated yield by the use of *N*-bromosuccinimide has been reported by Corey (*J. Amer. Chem. Soc.*, 1953, **75**, 2301).]

2-*Chloro*cyclo*heptanone*.—Chlorine was passed through a mixture of *cyclo*heptanone (52 g.), water (40 ml.), and calcium carbonate (24 g.) until all the carbonate had disappeared (*ca.* 2 hr.) (cf. Kötz, *Annalen*, 1913, **400**, 53). Throughout the reaction, the mixture was cooled in ice and

shaken at frequent intervals. Extraction with ether and fractionation gave 2-chloro*cyclo*heptanone (40 g., 59%), b. p. 100—103°/15 mm., n_D^{21} 1·4861 (Found: Cl, 24·2. Calc. for $C_7H_{11}OCl$: Cl, 24·2%). Treatment with Brady's reagent under the condition used for the bromo-ketone gave the 2 : 4-*dinitrophenylhydrazone* which crystallised from ethyl acetate in yellow needles, m. p. 140—141° (Found: C, 48·0; H, 4·65; N, 16·9; Cl, 10·6. $C_{13}H_{15}O_4N_4Cl$ requires C, 47·8; H, 4·65; N, 17·15; Cl, 10·85%). Light absorption in $CHCl_3$: $\lambda_{max.}$ 3580 Å, ε 24,800.

If the reaction mixture is not cooled or if chlorine is passed for a longer time, mainly 2 : 2(?)-*dichloro*cyclo*heptanone* (52 g., 62%), b. p. 128—130°/17 mm., n_D^{21} 1·5025 (Found: Cl, 38·9. $C_7H_{10}OCl_2$ requires Cl, 39·0%), is obtained.

cyclo*Hept*-2-*enone*.—(*a*) A rapidly stirred mixture of 2-bromo*cyclo*heptanone (100 g.) and collidine (85 g.) was heated to 180—185° for a few minutes in an oil-bath. As soon as the separation of collidine hydrobromide was complete, the bath was removed and benzene (300 ml.) was added to the now viscous reaction mixture when it had cooled to *ca.* 100°. The collidine hydrobromide was then filtered off and washed with hot benzene (200 ml.). The combined filtrates were washed with 2N-hydrochloric acid (200 ml.), the benzene layer was separated and dried (Na_2SO_4), and the solvent removed under reduced pressure. Fractionation of the residue gave a mixture of *cyclo*hept-2- (XI) and -3-enone (XII) (39 g., 68%), b. p. 31°/0·5 mm., n_D^{20} 1·491—1·500, $\lambda_{max.}$ 2270 Å (ε 5000—8000) in EtOH or C_6H_{14} (Found: C, 76·4; H, 9·3. Calc. for $C_7H_{10}O$: C, 76·3; H, 9·1%). The mixture of ketones (9 g.) formed a semicarbazone which after one recrystallisation from aqueous methanol formed plates (5 g.), m. p. 136—137°, $\lambda_{max.}$ 2270 (ε 9000) and 2650 Å (ε 7700) in EtOH (Found: C, 57·4; H, 7·7; N, 25·0. Calc. for $C_8H_{13}ON_3$: C, 57·5; H, 7·8; N, 25·1%). On further recrystallisation from aqueous methanol, the m. p. slowly rose and after 7 operations the *semicarbazone*, m. p. 155—156°, of *cyclo*hept-3-enone, was obtained; it had $\lambda_{max.}$ 2260 Å (ε 18,500) in EtOH (Found: C, 57·4; H, 7·8; N, 24·8%). Treatment of the mixture of ketones with Brady's reagent gave the 2 : 4-*dinitrophenylhydrazone* of *cyclo*hept-2-enone which, after chromatography on alumina in benzene–chloroform, crystallised from ethyl acetate–methanol in red plates, m. p. 122°, $\lambda_{max.}$ 3770 Å (ε 21,000) in $CHCl_3$ (Found: C, 53·7; H, 5·2; N, 19·0. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·9; N, 19·3%).

(*b*) A rapidly stirred mixture of 2-chloro*cyclo*heptanone (25 g.) and collidine (25 g.) was heated to about 220° and kept under gentle reflux. After about 2 hr., collidine hydrochloride began to separate and eventually the whole reaction mixture became viscous. After 2 hr., it was allowed to cool and worked up as above, giving *cyclo*heptenone (5 g., 27%), b. p. 26°/0·3 mm., n_D^{21} 1·4913, $\lambda_{max.}$ 2270 Å (ε 4800) in EtOH.

Hydrogenation of *cyclo*hept-2-enone (1·1 g.) in methanol (25 ml.) in the presence of platinic oxide resulted in the uptake of 240 ml. of hydrogen (at 20°/756 mm. Calc., 240 ml.), giving *cyclo*heptanone (1 g.), b. p. 71°/10 mm., n_D^{24} 1·4607; the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 148°.

3-*Bromo*cyclo*heptene*.—*cyclo*Heptene (32 g.; prepared from *cyclo*heptanone in nearly quantitative yield by reduction of lithium aluminium hydride in ether followed by dehydration with naphthalene-2-sulphonic acid; cf. Kohler *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 1057), *N*-bromosuccinimide (54·8 g.), benzoyl peroxide (0·2 g.), and carbon tetrachloride (200 ml.) were heated under reflux in nitrogen. An exothermic reaction set in after a few minutes and was complete after 1 hr. After cooling, succinimide was filtered off, the filtrate was washed with 5% sodium carbonate solution (100 ml.) and water, and dried (Na_2SO_4), and the solvent removed under reduced pressure. Fractionation gave 3-*bromo*cyclo*heptene* (25 g., 43%), b. p. 67°/8 mm., n_D^{22} 1·5281 (Found: C, 48·4; H, 6·5; Br, 45·7. $C_7H_{11}Br$ requires C, 48·0; H, 6·3; Br, 45·7%).

Bromo*cyclo*heptene was only partly hydrolysed by concentrated, boiling aqueous sodium carbonate, and oxidation of the product with sodium dichromate and sulphuric acid gave only a trace of *cyclo*heptenone.

cyclo*Hex*-2-*enone*.—*cyclo*Hexanone (98 g.) was brominated by the procedure used for *cyclo*heptanone, giving 2-bromo*cyclo*hexanone (51 g., 36%), b. p. 116°/15 mm. A rapidly stirred mixture of the bromo-ketone (8 g.) and collidine (8 g.) was heated to 175° for 3 min. Working up as in the case of *cyclo*hept-2-enone afforded *cyclo*hex-2-enone (1·8 g., 42%), b. p. 61—62°/10 mm., n_D^{22} 1·4897 (2 : 4-dinitrophenylhydrazone, m. p. 165°) (cf. Rigby, *J.*, 1949, 1587; Born, Pappo, and Szmuszkovicz, *J.*, 1953, 1779; Treibs, Franke, Leichsenring, and Rüder, *Ber.*, 1953, **86**, 616). When the dehydrobromination was carried out on a larger scale, however, extensive aromatisation took place and the product consisted of a mixture of *cyclo*hexenone and phenol.

3 : 3-*Dichloro*cyclo*heptene and Chloro*cyclo*hepta*-1 : 3-*diene*.—*cyclo*Hept-2-enone (60 g.) was added dropwise, with mechanical stirring, to phosphorus pentachloride (130 g.). Hydrogen chloride was vigorously evolved and the mixture was cooled in ice-water. After all the ketone had been added, stirring was continued for 2 hr. at 20° and for a further 2 hr. at 35—40°. The mixture was then added to ice-water (2 l.), and the products were extracted with ether. Distillation gave a range of fractions (total 50 g.), b. p. 56—104°/10 mm., n_D^{19} 1·513—1·518, consisting of chloro*cyclo*hepta-1 : 3-diene and mainly 3 : 3-dichloro*cyclo*heptene. They were added to a solution of potassium hydroxide (20 g.) in ethanol (100 ml.) at 35° and the mixture was then kept at 0° for 4 hr. The precipitate of potassium chloride (12 g.) was filtered off and washed with ether, and the filtrate was diluted with water (500 ml.) and extracted with ether. The combined ethereal solutions were dried (Na_2SO_4) and fractionated through a 6″ Fenske column, giving 1(or 2)-*chloro*cyclo*hepta*-1 : 3-*diene* (XIII or XIV) (18 g.), b. p. 61°/10 mm., n_D^{21} 1·5133, $\lambda_{max.}$ 2510 and 2570 Å, ε 4900 in C_6H_{14} (Found : C, 65·2; H, 7·4; Cl, 26·8. C_7H_9Cl requires C, 65·4; H, 7·0; Cl, 27·6%), and 3 : 3-*dichloro*cyclo*heptene* (11 g.), b. p. 102°/10 mm., n_D^{22} 1·5136 (Found : Cl, 42·4. $C_7H_{10}Cl_2$ requires Cl, 43·0%). Re-treatment of the dichloride with ethanolic potassium hydroxide gave a further 4 g. of 1-chloro*cyclo*hepta-1 : 3-diene, making a total yield of 22 g. (32%).

*Attempted Metallation of Chloro*cyclo*hepta*-1 : 3-*diene*.—The chloride (8 g.) was added to a stirred suspension of lithium (1·5 g.) in ether (170 ml.). After 2 hr., the solution became green and was then refluxed for 15 hr. Only 20—50% of the theoretical amount of lithium reacted in several experiments, and on carboxylation with solid carbon dioxide only traces of gummy, acidic products were obtained, the majority of the chloride being recovered unchanged.

2-*Chloro*-4-*methylpenta*-1 : 3-*diene* (XVI).—Mesityl oxide (98 g.) was added to a stirred solution of phosphorus pentachloride (250 g.) in carbon disulphide (150 ml.) at 0° (cf. Baeyer, *Annalen*, 1866, **140**, 298). The solution was then kept at 55—58° for 40 min. and poured on ice (100 g.). The carbon disulphide layer was separated, washed with sodium carbonate and water, dried ($CaCl_2$), and evaporated at ordinary pressure. The product was fractionated through an 8″ Dufton column, giving (i) 2-chloro-4-methylpenta-1 : 3-diene (27 g.), b. p. 34—36°/12 mm., n_D^{20} 1·4638, $\lambda_{max.}$ 2330 Å, ε 8100 in C_6H_{14} (Found : Cl, 29·8. Calc. for C_6H_9Cl : Cl, 30·4%), and (ii) 4 : 4-dichloro-2-methylpent-2-ene (31 g.), b. p. 60°/1 mm., n_D^{21} 1·4778.

Treatment of the dichloride with potassium hydroxide (10 g.) in ethanol (50 ml.) as above gave a further 12 g. of 2-chloro-4-methylpenta-1 : 3-diene, making a total yield of 39 g. (33%).

Metallation and Carboxylation of **2-*Chloro*-4-*methylpenta*-1 : 3-*diene***.—The chloro-diene (11 g.) in ether (10 ml.) was added dropwise to a vigorously stirred suspension of finely divided lithium (1·4 g.) in ether (170 ml.). After a few minutes, the solution became green and the lithium surface assumed a bright, metallic appearance. The mixture was gently refluxed for 14 hr. and then filtered through glass-wool into a flask containing excess of solid carbon dioxide (600 g.). About half of the theoretical amount of lithium had reacted. When the solution had attained room temperature, 0·1N-hydrochloric acid (100 ml.) was added, and the ethereal layer was separated and extracted with saturated aqueous sodium carbonate. The alkaline extract was acidified with hydrochloric acid and extracted with ether. Removal of the ether under reduced pressure gave a semi-solid product (1·5 g.) which could not be sublimed at 10^{-5} mm., but was purified by low-temperature crystallisation (−60°) from aqueous methanol. This afforded (?) **1 : 6 : 6-*trimethyl*-4-*oxo*-2-iso*propyl*cyclo*hex*-2-*enecarboxlic acid*** (XIX) (0·35 g., 1%), m. p. 187° (Found : C, 69·5; H, 9·2%; *M*, in camphor, 206; equiv. wt., by titration with sodium hydroxide, 246. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%; *M*, 224). Ultra-violet light absorption : $\lambda_{max.}$ 2430 Å, ε 10,300 in EtOH. Infra-red light absorption (Nujol mull) : $\nu_{max.}$ 1654 (vs; conjugated C=O stretching) and 1580 cm.$^{-1}$ (C=C stretching).

The yield of acid was consistently 1—1·5% in several runs. Only unchanged chloro-diene could be recovered from the neutral products and from attempted reactions of the lithium derivative with formaldehyde and benzophenone.

We thank the Department of Scientific and Industrial Research for a maintenance grant (to E. A. E.) and Dr. E. S. Waight, British Rubber Producers' Research Association, for the infra-red spectra.

Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, October 23rd*, 1953.]

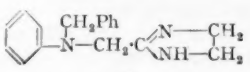
Meso-ionic Compounds derived from Pyridino(1′ : 2′-1 : 2)glyoxaline.

By N. W. Bristow, P. T. Charlton, D. A. Peak, and W. F. Short.

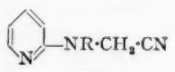
[Reprint Order No. 4748.]

The reactions of 2-pyridylaminoacetonitrile (II; R = H) show that it can also react as 5-aminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R = R′ = R″ = H). *N*-Alkyl- or *N*-aryl-*N*-2-pyridylaminoacetonitriles (II) afford acyl derivatives for which a meso-ionic structure (cf. VIII; R = Ac, Bz, or Ph·SO_2) is suggested.

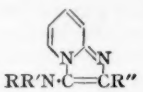
This investigation originated in a desire to prepare analogues of the antihistamine antazoline (I) in which the *N*-phenyl substituent is replaced by a 2-pyridyl group and the dihydroglyoxaline nucleus either remains or is replaced by an amidino-group. The starting point was 2-pyridylaminoacetonitrile (II; R = H), obtained from formaldehyde, sodium hydrogen sulphite, 2-aminopyridine, and sodium cyanide. On benzylation in chloroform solution this base afforded two monobenzyl derivatives, m. p. 83—84° and 100° respectively, and a dibenzyl derivative (picrate, m. p. 144°). The monobenzyl compound of lower m. p., obtained in 45% yield, afforded 2-benzylaminopyridine on oxidation with potassium permanganate and this indication that it is *N*-benzyl-*N*-2-pyridylaminoacetonitrile (II; R = Ph·CH_2) was confirmed by an independent synthesis (below). The other monobenzyl derivative and the dibenzyl compound arise from the capacity of 2-pyridylaminoacetonitrile to react in the tautomeric form (III; R = R′ = R″ = H). The structure of the monobenzyl compound, m. p. 100°, as (III; R = R″ = H, R′ = Ph·CH_2) follows from its hydrolysis to benzylamine and from its production by the catalytic reduction of 5-benzylideneaminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R″ = H, RR′ = Ph·CH:) ob-



(I)

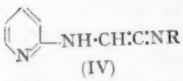


(II)



(III)

tained by the condensation of 2-pyridylaminoacetonitrile with benzaldehyde. Alternative formulæ for the benzylidene compound are excluded by the observation that it remains unchanged when heated with acetic anhydride. Reduction of the benzylidene derivative to the benzyl compound, m. p. 100°, shows that the latter cannot have the alternative structure (IV; R = Ph·CH_2). The dibenzyl compound obtained from 2-pyridylaminoacetonitrile is therefore regarded as 5-dibenzylaminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R″ = H, R = R′ = Ph·CH_2). A monobenzoyl derivative obtained from 2-pyridylaminoacetonitrile is also assigned a cyclic structure (III; R = R″ = H, R′ = Bz), since it is converted by reduction with lithium aluminium hydride into the benzyl compound, m. p. 100°.

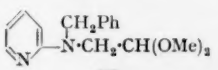


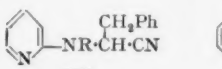
(IV)

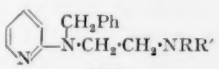
Acetylation of 2-pyridylaminoacetonitrile affords an acetyl derivative, m. p. 199°, also obtained by pyrolysis of 5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium chloride (below), and therefore regarded as 5-acetamidopyridino(1′ : 2′-1 : 2)glyoxaline (III; R = R″ = H, R′ = Ac). 2-Pyridylaminoacetonitrile and benzenesulphonyl chloride afford mono- and di-benzenesulphonyl derivatives, and since the first of these is soluble in aqueous sodium hydroxide it cannot have either of the structures (II; or IV; R = Ph·SO_2) but must have formula (III; R = R″ = H, R′ = Ph·SO_2) containing the ·SO_2·NH· group. The dibenzenesulphonyl derivative is consequently regarded as (III; R″ = H, R = R′ = Ph·SO_2). In accordance with these conclusions, the infra-red spectrum of the benzyl compound, m. p. 83—84°, showed an absorption band at 2250 $cm.^{-1}$ (in chloroform solution) due to the –CN group, whereas this band was absent from the spectrum of the benzyl compound, m. p. 100°. Absence of the –CN group was likewise indicated for the acetyl derivative of 2-pyridylaminoacetonitrile and of 2-pyridylaminoacetonitrile itself, showing

in the latter case that the cyclic tautomer (III; R = R′ = R″ = H) is the predominant form.

In an alternative synthesis of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (II; R = Ph·CH_2), 2-benzylamino-1 : 1-dimethoxyethane, prepared by a modification of the method of Rügheimer and Schön (*Ber.*, 1908, **41**, 17; cf. Jones, Kornfeld, McLaughlin, and Anderson, *J. Amer. Chem. Soc.*, 1949, **71**, 4001), was first condensed with 2-bromopyridine to give 2-(*N*-benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane (V), a compound subsequently prepared by Kaye (*J. Amer. Chem. Soc.*, 1951, **73**, 5467) by condensing 2-lithioaminopyridine with 2-chloro-1 : 1-dimethoxyethane and treating the resulting secondary amine with benzyl chloride and lithamide. 2-(*N*-Benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane was hydrolysed with 2N-hydrochloric acid, and the resultant aqueous solution of aldehyde was oximated to give *N*-benzyl-*N*-2-pyridylaminoacetaldoxime which was readily dehydrated by thionyl chloride to the nitrile (II; R = Ph·CH_2). This compound exhibited the properties of a normal nitrile in most of its reactions. For example, it was hydrolysed to the corresponding amide and acid, and afforded a dihydroglyoxaline on being heated with 2-aminoethylammonium toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497). Difficulties were encountered in attempting to convert the nitrile into the corresponding amidine, which could not be obtained by the Pinner method or by the action of sodamide. The nitrile was readily converted into the corresponding thioamide by the action of hydrogen sulphide in pyridine–triethylamine (Fairfull, Lowe, and Peak, *J.*, 1952, **742**) but aminating-desulphurisation with mercuriammonium chloride and alcoholic ammonia (cf. Bernthsen, *Ber.*, 1876, **9**, 429) gave very small and variable yields of amidine. The amidoxime, readily obtained from the nitrile and alcoholic hydroxylamine, gave a good yield of the amidinium chloride when reduced catalytically in alcoholic solution in presence of Raney nickel and ammonium chloride (cf. May and Baker, Ltd., Barber, and Self, B.P. 551,445). The same procedure also afforded α-(*N*-*p*-chlorobenzyl-*N*-2-pyridylamino)-acetamidine from *N*-*p*-chlorobenzyl-*N*-2-pyridylaminoacetonitrile. α-(*N*-Benzyl-*N*-2-pyridylamino)-*NN*′-diphenylacetamidine, prepared from 2-benzylaminopyridine and α-chloro-*NN*′-diphenylacetamidine, was recovered unchanged when heated with ammonium benzenesulphonate, ammonia, and aniline under conditions which usually result in the ammonolysis of *N*-phenylamidines (Oxley and Short, *J.*, 1949, 449).


(V)


(VI)

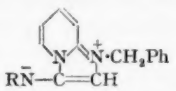
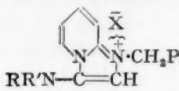

(VII)

N-Benzyl-*N*-2-pyridylaminoacetaldoxime and *N*-benzyl-*N*-2-pyridylaminoacetonitrile were both converted by acetic anhydride into an acetyl derivative of the nitrile, which from its infra-red spectrum no longer contained a –CN group. Since mild hydrolysis regenerated the nitrile, whereas energetic hydrolysis gave the corresponding acid, the possibility that this acetylation involves migration of the benzyl group from nitrogen to carbon giving the acetyl derivative (VI; R = Ac) or its cyclic tautomeride (III; R = Ac, R′ = H, R″ = Ph·CH_2) appeared unlikely, and it was eliminated by the synthesis of α-benzyl-α-2-pyridylaminoacetonitrile (VI; R = H) which afforded an entirely distinct acetyl derivative.

Mignonac and Hoffmann (*Compt. rend.*, 1930, **191**, 718) obtained a compound from sodiobenzyl cyanide and benzoyl chloride to which they assigned the structure Bz·CPh:C:NBz although their evidence does not appear to exclude the alternative structure BzO·CPh:CPh·CN. The analogous formula, $C_5H_4N{\cdot}N(CH_2Ph){\cdot}CH{:}C{:}NAc$, for our acetyl derivative must be rejected since the tetrahydro-derivative obtained by catalytic reduction is not *N*′-acetyl-*N*-benzyl-*N*-2-pyridylethylenediamine (VII; R = H, R′ = Ac). The latter compound was obtained by reduction of *N*-benzyl-*N*-2-pyridylaminoacetonitrile with lithium aluminium hydride to the amine (VII; R = R′ = H), acetylation of which gave a mixture of the mono- and the di-acetyl (VII; R = R′ = Ac) derivatives. Phthaloylation of the amine gave [VII; RR′ = $(CO)_2C_6H_4$], also obtained from *N*-2-bromoethylphthalimide and 2-benzylaminopyridine. Reduction of the diacetyl derivative (VII;

R = R′ = Ac) with lithium aluminium hydride gave *N*-benzyl-*NN*′-diethyl-*N*-2-pyridylethylenediamine (VII; R = R′ = Et), also obtained from 2-benzylaminopyridine and 2-diethylaminoethyl chloride.

The production of the acetyl derivative cannot involve migration of the hydrogen atom at position 3 of the pyridine nucleus, because a similar acetyl derivative was prepared containing a methyl group in this position. Likewise the *ortho*-positions in the benzyl nucleus are not involved since an acetyl derivative was also obtained from a nitrile containing a mesitylmethyl group in the place of the benzyl group. We therefore propose a meso-ionic structure for the acetyl derivative, one of the contributing ionic forms, which may be called anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium hydroxide, being represented by formula (VIII; R = Ac). A similar meso-ionic ring structure, containing two nitrogen, two carbon, and one oxygen atom, was first proposed for the sydnones (Baker, Ollis, and Poole, *J.*, 1949, 307; 1950, 1542; Hill and Sutton, *J.*, 1949, 746). We cannot offer a formal proof of structure (VIII), which, however, rests on the

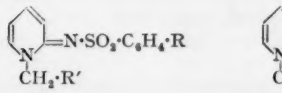
(VIII)   (IX)

exclusion of simpler alternatives and accounts satisfactorily for the formation and reactions of the compound. Thus, the acetyl derivative yields a hydrochloride, which would be a quaternary ammonium salt (IX; R = Ac, R′ = H, X = Cl), and, in agreement with this formula, decomposes on being heated, benzyl chloride and 5-acetamidopyridino(1′ : 2′-1 : 2)-glyoxaline (III; R = R″ = H, R′ = Ac) being formed. Methyl iodide in boiling acetone converts the acetyl derivative into a quaternary salt which is formulated as (IX; R = Me, R′ = Ac, X = I) since hydrolysis with boiling dilute sulphuric acid gives a 93% yield of methylamine. This suggests either that the structure (VIII; R = Ac) makes the largest contribution to the meso-ionic system or that, if the structure containing the group $^-$O·CMe:N· is predominant, the *O*-methyl derivative MeO·CMe:N· must immediately and completely isomerise to the *N*-methyl derivative. Hydrolysis of the quaternary salt with cold alcoholic hydrochloric acid removes the acetyl group and gives 3-benzyl-5-methylaminopyridino(1′ : 2′-1 : 2)glyoxalinium iodide (IX; R = Me, R′ = H, X = I), which is also formed directly at room temperature from the acetyl derivative (VIII; R = Ac) and methyl iodide in methanol, the acetyl group being eliminated. The presence of a benzyl group is not essential for the production of compounds of type (VIII), a number of analogues in which the benzyl group is replaced by phenyl, ethyl, 2-pyridyl, or 2-thienylmethyl radicals being readily prepared, usually by the route proceeding *via* the acetal and acetaldoxime (above). Meso-ionic compounds containing other acyl groups in place of the acetyl group were also prepared. For example, a benzoyl derivative (VIII; R = Bz) was obtained by the action of benzoyl chloride and pyridine either on *N*-benzyl-*N*-2-pyridylaminoacetaldoxime or on *N*-benzyl-*N*-2-pyridylaminoacetonitrile. A benzenesulphonyl derivative (VIII; R = Ph·SO_2), obtained from the nitrile and benzenesulphonyl chloride in pyridine was insoluble in alkali, showing that the ·NH·SO_2· group is absent. The benzenesulphonyl derivative gave a sulphonmethylamido-compound (IX; R = Ph·SO_2, R′ = Me, X = I) with methyl iodide in boiling alcoholic solution.

All these meso-ionic compounds exhibited a strong green fluorescence in ultra-violet light in chloroform solution but not in dilute hydrochloric acid solution. This was in marked contrast to the non-meso-ionic intermediates, most of which exhibited blue fluorescence in dilute hydrochloric acid solution but none in chloroform solution.

In connection with the elucidation of the structure of the arenesulphonyl derivatives we made some interesting observations on the reaction of 2-arenesulphonamidopyridines with chloroacetamide and chloroacetonitrile. Phillips (*Nature*, 1941, **148**, 409, 466) states that sulphapyridine, chloroacetamide, and alkali yield *N*-2-pyridyl-*N*-sulphanilylglycineamide which is hydrolysed by alkali to *N*-2-pyridyl-*N*-sulphanilylglycine, which affords 2-pyridylglycine with hot mineral acid. The introduction of the acetamide and acetonitrile residues into the ·SO_2NH· group seemed surprising in view of Kelly and Short's finding (*J.*, 1945,

242) that sulphapyridine is alkylated at the pyridine-nitrogen atom, giving 1-alkyl-1 : 2-dihydro-2-iminopyridines. Repetition of the condensation of sulphapyridine and chloroacetamide gave, as the only isolated products of the reaction, 15% of recovered sulphapyridine and a 62% yield of 1-carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine (X; R = NH_2, R′ = $CO{\cdot}NH_2$), the structure of which was demonstrated by hydrolysis to 4-hydroxypyridino(1′ : 2′-1 : 2)glyoxaline (XI). The latter compound was first prepared by Reindel (*Ber.*, 1924, **57**, 1381) by cyclisation of the condensation product of 2-amino-



pyridine and chloroacetic acid, the structure of which was shown by Tschitschibabin (*ibid.*, pp. 1168, 2092) to be 1-carboxymethyl-1 : 2-dihydro-2-iminopyridine. Condensation has therefore occurred mainly on the pyridine nitrogen atom as expected. In boiling acetic anhydride, (X; R = NH_2, R′ = $CO{\cdot}NH_2$) cyclised with elimination of the sulphanilyl group to a compound formulated as 4-acetamidopyridino(1′ : 2′-1 : 2)glyoxaline. The same compound was obtained from the condensation product of 2-toluene-*p*-sulphonamidopyridine and chloroacetamide which must therefore have the structure (X; R = Me, R′ = $CO{\cdot}NH_2$). Condensation of 2-toluene-*p*-sulphonamidopyridine with chloroacetonitrile gave a compound presumably of the analogous structure (X; R = Me, R′ = CN).

Experimental

2-Pyridylaminoacetonitrile.—The conditions of reaction for this preparation have been studied in some detail, and the best yield was obtained under the following conditions.

A mixture of formalin (120 c.c., 1·5 mols.), sodium hydrogen sulphite (156 g., 1·5 mols.), and water (300 c.c.) was stirred for 0·5 hr., then heated to 95°, and 2-aminopyridine (141 g., 1·5 mols.) was added and stirring was continued for an hour. Sodium cyanide (150 g., 3 mols.) in water (300 c.c.) was run in, and heating and stirring were continued for 4 hr. The dark solution was cooled, then filtered from crystals of sodium sulphite, and the filtrate thoroughly extracted with chloroform (6 × 500 c.c.). The combined chloroform extracts were dried ($CaCl_2$) and evaporated, finally under reduced pressure. The brown solid residue was crystallised from ethyl acetate (600 c.c.), giving 90 g. (45%) of brown prisms, m. p. 123—124°.

The use of an equimolecular amount of sodium cyanide gave a lower yield, and an increase in the time of heating after the addition of the cyanide did not increase the yield. Material of this quality was suitable for most preparative purposes. If a purer material was required the following procedure was used.

The crude nitrile was distilled and the fraction of b. p. 155—160°/1·1 mm. (83·5%) was collected as a yellow-green mixture of crystals and oil. Trituration with a little benzene afforded the pure *nitrile* as pale yellow prisms (60%), m. p. 126° unchanged by recrystallisation from acetone–benzene (Found: N, 31·4. $C_7H_7N_3$ requires N, 31·6%). The *picrate* separated from 50% methanol in yellow rods, m. p. 209° (Found: N, 23·5. $C_{13}H_{10}O_7N_6$ requires N, 23·2%). The *hydrochloride* crystallised from *iso*propanol in yellow needles, m. p. 152—153° (Found: N, 24·5. $C_7H_8N_3Cl$ requires N, 24·8%). The *tartrate* separated from aqueous acetone in colourless hydrated needles, m. p. 125—126°, which, after drying, melted at 151° (Found, on dried material: C, 46·4; H, 4·8; N, 15·0. $C_{11}H_{13}O_6N_3$ requires C, 46·6; H, 4·6; N, 14·8%).

The nitrile deteriorated on storage and became black and tarry after a few months even when kept in tightly stoppered bottles.

5-Acetamidopyridino(1′ : 2′-1 : 2)glyoxaline (III; R = H, R′ = Ac).—2-Pyridylaminoacetonitrile (4·7 g.) was heated under reflux with acetic anhydride (25 c.c.) for 50 min. The cooled solution was poured on ice and basified, the *acetyl* derivative separating in long needles. Recrystallisation from *iso*propanol gave 3·9 g. (63%), m. p. 196—199°, raised to m. p. 199° by recrystallisation from water (Found: C, 62·1; H, 5·1; N, 23·6. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0%). A further 0·9 g. (13%), m. p. 197—199°, was obtained by chloroform extraction of the combined mother-liquors.

5-Benzamidopyridino(1′ : 2′-1 : 2)glyoxaline.—A mixture of 2-pyridylaminoacetonitrile (6·65 g.), benzoyl chloride (6·9 g.), and pyridine (50 c.c.) was heated for a short time on the steam-bath,

cooled, and filtered. The resultant hydrochloride was washed with pyridine and acetone, and the free base precipitated from dilute aqueous alkaline solution by carbon dioxide. Crystallisation from ethanol gave the *base* as thin solvated prisms which, after drying *in vacuo* at 78° (Found: loss in weight, 16·0. $C_{14}H_{11}ON_3,C_2H_5{\cdot}OH$ requires loss in weight, 16·3%), had m. p. 170° (8·1 g., 68%) (Found: C, 71·3; H, 4·6; N, 17·7. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·7; N, 17·7%). Some early preparations of this compound originally had m. p. 157° but this changed gradually to 170°. The *hydrochloride* separated from water as needles, m. p. 295—296° (decomp.) (Found: C, 61·5; H, 4·5; N, 15·5. $C_{14}H_{12}ON_3Cl$ requires C, 61·4; H, 4·4; N, 15·4%). The *picrate* separated from nitrobenzene in needles, m. p. 264° (decomp.) (dependent upon the rate of heating) (Found: N, 18·3. $C_{20}H_{14}O_8N_6$ requires N, 18·0%).

When the acylation was carried out with benzoic anhydride instead of benzoyl chloride the yield was less than 2%.

5-Benzenesulphonamido- and 5-Dibenzenesulphonamido-pyridino(1′ : 2′-1 : 2)*glyoxaline*.—Benzenesulphonyl chloride (9·5 g.) was added in portions to 2-pyridylaminoacetonitrile (7·15 g.) in anhydrous pyridine (25 c.c.), so that the temperature did not exceed 50°. The solid which separated overnight was filtered off and washed with a little methanol, giving the *dibenzenesulphonyl* derivative as large pale-yellow prisms (3·4 g.), m. p. 165° (decomp.). Crystallisation from acetone–ether gave large colourless prisms of unchanged m. p. (Found: C, 55·4; H, 3·6; N, 9·5. $C_{19}H_{15}O_4N_3S_2$ requires C, 55·2; H, 3·6; N, 10·15%). It was insoluble in water and in dilute sodium hydroxide.

The pyridine filtrate was poured into water (4 vols.) and stirred until the precipitate solidified. The dried solid was extracted with boiling acetone (2 × 30 c.c.), and the combined extracts were concentrated to half volume and diluted with ether (30 c.c.), another 1·2 g. of the dibenzenesulphonyl derivative, m. p. 165°, being slowly precipitated.

The brown powder insoluble in acetone was shaken with water (50 c.c.) and N-sodium hydroxide (20 c.c.), filtered from a little insoluble solid, and neutralised with N-hydrochloric acid (20 c.c.). Crystallisation of the buff solid (4·1 g.) from *n*-butanol afforded the *monobenzenesulphonyl* derivative as pale-green rods, m. p. 212° (decomp.) (Found: N, 15·8. $C_{13}H_{11}O_2N_3S$ requires N, 15·4%). The compound was insoluble in water but was soluble in both dilute hydrochloric acid and dilute sodium hydroxide.

5-Benzylideneaminopyridino(1′ : 2′-1 : 2)*glyoxaline*.—A mixture of 2-pyridylaminoacetonitrile (5·32 g.) and benzaldehyde (4·25 g.) was heated at 100° for 1 hr., cooled, ground with ether, and filtered, giving 4·95 g. of a brown solid, m. p. 102°. Two recrystallisations from light petroleum (b. p. 80—100°) gave *5-benzylideneaminopyridino*(1′ : 2′-1 : 2)*glyoxaline* as sheaves of yellow-brown needles (4·53 g., 51%), m. p. 114° (Found: C, 76·0; H, 5·0; N, 18·8. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0; N, 19·0%). The compound (96%) was recovered after 2 hours' heating with acetic anhydride at 100°.

5-Benzylaminopyridino(1′ : 2′-1 : 2)*glyoxaline*.—(*a*) 5-Benzamidopyridino(1′ : 2′-1 : 2)glyoxaline (1·0 g.) in dry tetrahydrofuran (15 c.c.) was added to a solution of lithium aluminium hydride (0·24 g.) in ether (15 c.c.), and the mixture was refluxed for 0·5 hr. The excess of hydride was decomposed with ethyl acetate and a few drops of aqueous sodium hydroxide, and the resulting suspension was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was crystallised from acetone giving, after some concentration, starting material (0·70 g.), m. p. 169·5°. Addition of picric acid to the filtrate gave a crude picrate (0·30 g.), a hot alcoholic extract of which, on cooling, deposited *5-benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxalinium picrate* (70 mg.), m. p. 180—181°, undepressed on admixture with the picrate prepared as in (*b*) below (Found: C, 53·8; H, 3·8; N, 18·7. $C_{20}H_{16}O_7N_6$ requires C, 53·1; H, 3·6; N, 18·6%).

(*b*) 5-Benzylideneaminopyridino(1′ : 2′-1 : 2)glyoxaline (5·9 g.) in methanol (50 c.c.) was hydrogenated at room temperature and pressure with palladium–charcoal (0·3 g. of 10%) as catalyst; approx. 1 mol. of hydrogen was absorbed and the final solution was almost colourless. The filtered solution was evaporated to a brown syrup which gradually crystallised. The solid separated from acetone as yellow-brown plates (2·8 g., 47%), m. p. 100°, and a further recrystallisation (charcoal) afforded *5-benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline* as large yellow plates, m. p. 100° (Found: C, 75·2; H, 6·0; N, 18·7. $C_{14}H_{13}N_3$ requires C, 75·3; H, 6·0; N, 18·8%). The picrate separated from ethanol in needles, m. p. 182·5°.

Hydrolysis was effected by 5N-sulphuric acid for 1·5 hr. on the steam-bath. The cooled solution was basified and the resultant benzylamine isolated with ether and characterised as the picrate, m. p. and mixed m. p. 197°.

Benzylation of 2-Pyridylaminoacetonitrile.—(a) *N-Benzyl-N-2-pyridylaminoacetonitrile*. 2-Pyridylaminoacetonitrile (12·3 g.) and benzyl chloride (11·7 g.) were refluxed together in dry

chloroform (60 c.c.). A heavy oil separated after 15 min. but this largely redissolved after 24 hours' heating. The mixture was cooled and poured into ether (300 c.c.), the ether decanted from the gummy precipitate, and the product washed with ether by stirring and decantation. The dark gum was dissolved in warm *iso*propanol (50 c.c.), and the solution was kept at 0° for a day. The solid which separated was filtered off and washed with *iso*propanol until colourless, giving 8·55 g. (36%), m. p. 209°. Recrystallisation from *iso*propanol gave colourless needles of the *hydrochloride*, m. p. 214° (Found : N, 16·2. $C_{14}H_{14}N_3Cl$ requires N, 16·2%).

During the course of several preparations it was found that if seeds were added the crystalline hydrochloride separated directly from the reaction mixture in chloroform. After 6 hours' heating the mixture was cooled and the hydrochloride (28%) was collected. No more solid separated after heating of the filtrate under reflux for a further 16 hr. By addition of the cooled solution to excess of ether and crystallisation of the precipitated gum from ethanol–acetone a further crop of crystals was obtained, bringing the total yield of the salt to 45%.

The *picrate* crystallised from ethanol in plates, m. p. 149·5° (Found : C, 53·3; H, 3·55; N, 18·5; picric acid, 50·2. $C_{20}H_{16}O_7N_6$ requires C, 53·1; H, 3·6; N, 18·6; picric acid, 50·65%). The *toluene*-p-*sulphonate* separated from 80% ethanol as colourless prisms, m. p. 204° (Found : N, 10·7. $C_{21}H_{21}O_3N_3S$ requires N, 10·6%). The *base* separated slowly when an aqueous solution of the hydrochloride was made strongly alkaline with 5N-sodium hydroxide. Crystallisation from light petroleum (b. p. 60—80°) or ethanol afforded colourless needles, m. p. 83—84° (Found : C, 75·3; H, 5·8; N, 19·0. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·85%).

(b) 5-*Benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline.* The *iso*propanol mother-liquors from several benzylation reactions [see under (a)] were combined and poured into ether (5 vols.). The sticky brown precipitate was dissolved in water, and aqueous lithium picrate solution was added until precipitation was complete. The gummy precipitate, which hardened on stirring, was crystallised from 60% ethanol to give a yellow-brown mixture of picrates.

The mixture (69 g.) was extracted with hot chloroform (10 vols.), and the suspension cooled and filtered. The insoluble residue (42 g.) was refluxed with acetone (200 c.c.), cooled, and filtered. The filtrate was evaporated to dryness and the residual picrate recrystallised from 70% ethanol (300 c.c.) in yellow-brown plates (9·75 g.), m. p. 182—183°, raised to 184° by a further crystallisation.

The picrate was shaken with aqueous lithium hydroxide and ether until dissolved, the ether evaporated, and the base recrystallised from light petroleum (b. p. 80—100°) to give yellow plates, m. p. 100°.

Both the base and the picrate were undepressed in m. p. on admixture with 5-benzylaminopyridino(1′ : 2′-1 : 2)glyoxaline and its picrate respectively, obtained by catalytic reduction of the benzylidene derivative of 2-pyridylaminoacetonitrile.

(c) 5-*Dibenzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline.* The chloroform solution above was concentrated to 200 c.c. and diluted with ether (400 c.c.). The dark oily precipitate solidified when boiled with ethanol (50 c.c.), and the suspension was filtered hot; a dark tar separated from the filtrate. The solid on the filter was washed with hot ethanol to remove tars and then crystallised from ethanol, giving yellow needles of the *picrate*, m. p. 154° (Found : C, 59·2; H, 4·1; N, 15·1; picric acid, 42·35. $C_{27}H_{22}O_7N_6$ requires C, 59·8; H, 4·1; N, 15·5; picric acid, 42·25%). Attempts to isolate the base from the picrate were unsuccessful.

Oxidation of N-*Benzyl*-N-2-*pyridylaminoacetonitrile.*—A saturated solution of potassium permanganate in 70% acetone was added to a solution of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (1·0 g.) in acetone (7 c.c.) and 5N-sulphuric acid (3 c.c.) until the reaction became sluggish; about 10 c.c. were required. The filtered solution was diluted with water and basified, giving 2-benzylaminopyridine (0·41 g., 50%), m. p. 93—94°, undepressed on admixture with an authentic sample, m. p. 94°. A similar result was obtained by the oxidation of *N*-benzyl-*N*-2-pyridylaminoacetaldoxime.

Hydrolysis of N-*Benzyl*-N-2-*pyridylaminoacetonitrile.*—The nitrile hydrochloride (2·60 g.) was dissolved in 10% hydrogen peroxide (15 c.c.), and 5N-sodium hydroxide (4 c.c.) was added dropwise. The precipitated gum was crystallised from ethanol (2 c.c.), and the crystals, together with those which separated from the supernatant liquid during 3 days, were extracted with boiling light petroleum (b. p. 80—100°) (3 × 5 c.c.). The residue was recrystallised from ethanol, affording α-(*N-benzyl*-N-2-*pyridylamino*)*acetamide* (0·11 g., 5%) as prisms, m. p. 139·5° (Found : C, 69·45; H, 5·8; N, 17·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). The *picrate* separated from ethanol in needles, m. p. 155° (decomp.) (Found : N, 17·5. $C_{20}H_{18}O_8N_6$ requires N, 17·9%).

Heating the nitrile with 5N-hydrochloric acid for 1·5 hr. at 95° afforded *N*-benzyl-*N*-2-

pyridylaminoacetic acid, isolated as the *sodium* salt (44%), needles [from ethanol–ether (3 : 1)], m. p. 300° (Found: N, 10·1; Na, 8·4. $C_{14}H_{13}O_2N_2Na$ requires N, 10·6; Na, 8·7%). The *benzylammonium* salt crystallised from water in prisms, m. p. 165° (Found: C, 71·5; H, 6·4; N, 12·0. $C_{21}H_{23}O_2N_3$ requires C, 72·2; H, 6·6; N, 12·0%).

Heating the nitrile (6·0 g.) with ethanol (12 c.c.) and sulphuric acid (1·8 c.c.) for 5 hr. under reflux afforded *ethyl* N-*benzyl*-N-2-*pyridylaminoacetate* (2·0 g., 28%), long needles [from light petroleum (b. p. 60—80°)], m. p. 72° (Found: C, 71·8; H, 6·5; N, 10·7. $C_{16}H_{18}O_2N_2$ requires C, 71·1; H, 6·7; N, 10·4%).

Alternative Synthesis of N-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—2-Bromo-1 : 1-dimethoxyethane (391 g.) (Bedoukian, *J. Amer. Chem. Soc.*, 1944, **66**, 651) was added (2 hr.) with stirring to benzylamine (550 g.) kept at 120—130° by an oil-bath at 100—105°. The bath-temperature was maintained for a further 45 min. and then the reaction mixture was allowed to cool to 80° and poured into benzene (2 l.). Filtration removed benzylammonium bromide (427 g., 98%). The filtrate was distilled under reduced pressure to give benzene, benzylamine (55 g.), and 2-benzylamino-1 : 1-dimethoxyethane (344 g., 76%), b. p. 102°/1 mm.

A mixture of 2-benzylamino-1 : 1-dimethoxyethane (97·5 g.), 2-bromopyridine (79 g.), and anhydrous potassium carbonate (140 g.) was stirred and heated in an ethylene glycol vapour bath for 19 hr. The filtered mixture was distilled, giving 2-(*N*-benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane (V) (89 g., 65%), b. p. 155—160°/1 mm., m. p. 50° (Found: C, 70·3; H, 7·05; N, 10·1. Calc. for $C_{16}H_{20}O_2N_2$: C, 70·6; H, 7·4; N, 10·3%). The *picrate* separated from alcohol in plates, m. p. 119° (Found: N, 14·2. $C_{22}H_{23}O_9N_5$ requires N, 14·0%). 2-Benzylamino-1 : 1-dimethoxyethane (24 g., 25%) was recovered.

The acetal (V) (27 g.) was dissolved in 2·1N-hydrochloric acid (107 c.c.), and the solution was heated on the steam-bath for 1·5 hr. [The *aldehyde picrate* could be isolated from this solution by neutralisation with lithium hydroxide and addition of an equivalent of aqueous lithium picrate solution. It separated from ethanol in prisms, m. p. 144° (Found: C, 52·15; H, 4·0; N, 15·6. $C_{20}H_{17}O_8N_5$ requires C, 52·8; H, 3·8; N, 15·4%).] Anhydrous sodium acetate (37 g.) and hydroxylamine hydrochloride (28 g.) were dissolved in the hot solution, which was then stored at room temperature for 2 days and poured into excess of saturated aqueous sodium carbonate. The precipitated gum was washed by decantation and boiled with a little ethanol, whereupon N-*benzyl*-N-2-*pyridylaminoacetaldoxime* crystallised in rhombs (20 g., 85%), m. p. 114° (Found: C, 70·3; H, 6·3; N, 17·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). The *hydrochloride* separated from alcohol–ether in aggregates of crystals, m. p. 142° (Found: N, 15·0. $C_{14}H_{16}ON_3Cl$ requires N, 15·1%). The *picrate* separated from ethanol in rhombs, m. p. 134° (Found: N, 17·8. $C_{20}H_{18}O_8N_6$ requires N, 17·9%).

A solution of thionyl chloride (3·57 g.) in dry chloroform (10 c.c.) was slowly added to a suspension of the aldoxime (7·23 g.) in dry chloroform (30 c.c.). After the exothermic reaction had subsided, the mixture was heated under reflux for 15 min. and cooled. Dilution with ether precipitated a thick dark oil which was washed with ether and dissolved in water, and the solution was extracted with chloroform, which removed most of the colour. A solution of sodium toluene-*p*-sulphonate (6 g.) in water (25 c.c.) was added to the aqueous layer and the resulting precipitate (8·25 g., 69%; m. p. 192—195°) was recrystallised from 80% ethanol, giving *N*-benzyl-*N*-2-pyridylaminoacetonitrile toluene-*p*-sulphonate as prisms, m. p. 204°.

The toluene-*p*-sulphonate (7·9 g.) was dissolved in hot 75% methanol (40 c.c.) and 5N-sodium hydroxide (24 c.c.), and diluted with cold water (150 c.c.) and ice (20 g.). After 1 hr. at 0° the precipitate was collected and extracted with hot light petroleum (b. p. 80—100°) which left a residue (1·3 g., 16%) of the starting material. The cooled petroleum solution deposited *N*-benzyl-*N*-2-pyridylaminoacetonitrile (1·95 g., 44%), m. p. 83·5°, undepressed by the product prepared by the benzylation of 2-pyridylaminoacetonitrile. A further 1·0 g. (22%) of the nitrile separated from the aqueous-methanolic filtrate after 24 hr. at 0°.

2-(N-*Benzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline*.—*N*-Benzyl-*N*-2-pyridylaminoacetonitrile (4·75 g.) was heated with 2-aminoethylammonium toluene-*p*-sulphonate (5·45 g.) at 145° for 3·5 hr. The hot mixture was diluted with ethanol (15 c.c.) and set aside at room temperature for 2 hr. Filtration yielded the nitrile toluene-*p*-sulphonate (2·40 g., 29%), m. p. and mixed m. p. 203·5°. The filtrate was diluted with water, basified, and extracted with benzene. The extract was washed with water, dried, and evaporated to give 2-(N-*benzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline* (2·80 g., 50%), m. p. 105°. Recrystallisation from light petroleum (b. p. 80—100°) gave prisms, m. p. 108° (Found: N, 20·6. $C_{16}H_{18}N_4$ requires N, 21·0%).

N-*Benzyl*-N-2-*pyridylamino*(*thioacetamide*).—Treating *N*-benzyl-*N*-2-pyridylaminoacetonitrile with hydrogen sulphide in triethylamine–pyridine solution (Fairfull *et al.*, *loc. cit.*) afforded

N-*benzyl*-N-2-*pyridylamino*(*thioacetamide*) (85%) as prisms (from ethanol), m. p. 157° (Found : C, 66·0; H, 5·7; N, 16·1. $C_{14}H_{15}N_3S$ requires C, 65·3; H, 5·9; N, 16·3%).

N-*Benzyl*-N-2-*pyridylaminoacetamidoxime*.—A mixture of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (11·0 g.), hydroxylamine hydrochloride (3·5 g.), sodium hydroxide (2·0 g.), ethanol (75 c.c.), and water (3 c.c.) was heated at 100° for 4 hr. in a glass pressure-bottle. The amber solution, when filtered and chilled overnight, deposited a mass of crystals (8·5 g., 68%), m. p. 128°. Recrystallisation from ethanol gave the *amidoxime* as colourless rods, m. p. 129—131° (Found : C, 65·6; H, 6·2; N, 21·4. $C_{14}H_{16}ON_4$ requires C, 65·6; H, 6·25; N, 21·9%).

α-(N-*Benzyl*-N-2-*pyridylamino*)*acetamidine*.—(*a*) A mixture of *N*-benzyl-*N*-2-pyridylamino(thioacetamide) (1·0 g.), mercuriammonium chloride (3·0 g.), absolute ethanol (100 c.c.), and 5N-alcoholic ammonia (3 c.c.) was shaken at room temperature for 4 days. The filtered solution was evaporated to give a residue which was extracted with hot light petroleum (b. p. 80—100°). *N*-Benzyl-*N*-2-pyridylaminoacetonitrile (0·51 g.; m. p. 84°) was deposited on cooling. The residue from the extraction was dissolved in absolute ethanol, filtered from ammonium chloride, and diluted with dry ether to precipitate the nitrile hydrochloride (0·12 g.), m. p. 204°. The alcoholic mother-liquors were diluted with water and mixed with aqueous lithium picrate; the *amidine picrate* then separated in needles, which on recrystallisation from acetonitrile had m. p. 167° (Found : C, 51·35; H, 3·9; N, 21·3. $C_{20}H_{19}O_7N_7$ requires C, 51·2; H, 4·1; N, 20·9%). The best yield was 0·04 g. (2%).

(*b*) A mixture of *N*-benzyl-*N*-2-pyridylaminoacetamidoxime (5·0 g.), methanol (40 c.c.), water (10 c.c.), and ammonium chloride (1·05 g.) was hydrogenated (Raney nickel catalyst, 1·0 g.) at 60°/30 atm. for 4 hr. When cold, the resulting ammoniacal solution was filtered from catalyst and evaporated to dryness under reduced pressure, giving a yellow gum which was readily soluble in water. The picrate separated from ethanol in bunches of yellow needles, m. p. 168° (decomp.), and m. p. 167° on admixture with the picrate (m. p. 167°) obtained as above. The *toluene*-p-*sulphonate* crystallised from *iso*propanol in colourless needles, m. p. 166° (Found : C, 61·7; H, 5·7; N, 13·3. $C_{21}H_{24}O_3N_4S$ requires C, 61·15; H, 5·9; N, 13·6%). When a solution of the toluene-*p*-sulphonate in dilute hydrochloric acid was quickly made alkaline with sodium hydroxide solution a crystalline precipitate of the free *amidine* was obtained, having m. p. 124—125° (Found : N, 23·0. $C_{14}H_{16}N_4$ requires N, 23·3%). When a dilute solution of the toluene-*p*-sulphonate in water was made alkaline no immediate precipitation occurred, but after several hours colourless needles of *N*-benzyl-*N*-2-pyridylaminoacetamide separated, having m. p. 139° alone or mixed with the hydrolysis product of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (Found : C, 69·6; H, 6·2; N, 17·5%).

N-p-*Chlorobenzyl*-N-2-*pyridylaminoacetonitrile*.—2-Pyridylaminoacetonitrile (30 g.) and *p*-chlorobenzyl chloride (36·4 g.) were heated under reflux in dry chloroform (180 c.c.). After about an hour a heavy oil separated and the mixture was then seeded and heating continued for 2·5 hr. The oil gradually crystallised and, next day, the solid was collected and washed with chloroform, giving 20·5 g. (31%) of yellow plates, m. p. 208—209°. Recrystallisation from a mixture of ethanol (35 c.c.) and ethyl acetate (60 c.c.) afforded colourless plates of the *hydrochloride* (16·5 g., 25%), m. p. 211—212° (Found : N, 14·6. $C_{14}H_{13}N_3Cl_2$ requires N, 14·3%). The free *base* separated slowly in cream needles when an equivalent of N-sodium hydroxide was added to an aqueous solution of the hydrochloride. Two recrystallisations from light petroleum (b. p. 60—80°) afforded colourless needles, m. p. 83—84° (Found : N, 16·4. $C_{14}H_{12}N_3Cl$ requires N, 16·3%).

2-(N-p-*Chlorobenzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline*.—*N*-*p*-Chlorobenzyl-*N*-2-pyridylaminoacetonitrile (5·15 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (4·64 g.) were heated together at 145° for 45 min. and then at 150° for 15 min. Ammonia was evolved rapidly above 140°. The cooled product was dissolved in warm methanol (10 c.c.) and added to water (50 c.c.) and 5N-sodium hydroxide (10 c.c.). The dark oil which was precipitated solidified on stirring. The solid was collected and suspended in water, and dilute hydrochloric acid was added with stirring until the solution was permanently acid to Congo-red paper. The solution was filtered, decolorised with charcoal, and made alkaline; the precipitated oil soon solidified (4·1 g., 68%). The crude dihydroglyoxaline was reconverted into the *toluene*-p-*sulphonate* (57%) which, after two crystallisations from ethyl acetate containing a little ethanol, melted at 161—162° (Found : N, 11·6. $C_{23}H_{25}O_3N_4ClS$ requires N, 11·85%).

α-(N-p-*Chlorobenzyl*-N-2-*pyridylamino*)*acetamidine*.—Sodium hydroxide (2·06 g.) in water (5 c.c.) was added slowly, with cooling and stirring to a suspension of *N*-*p*-chlorobenzyl-*N*-2-pyridylaminoacetonitrile (13·3 g.) and hydroxylamine hydrochloride (3·62 g.) in ethanol (50 c.c.). The mixture was heated in a glass pressure-bottle at 100° for 4·5 hr. and filtered hot

from sodium chloride, and the filtrate was then chilled overnight. The amidoxime separated in colourless needles (8·5 g., 57%), m. p. 166° after two crystallisations from ethanol. The compound appeared to be solvated and analytical results were unsatisfactory.

A mixture of the amidoxime (8·1 g.) in methanol (60 c.c.) and of ammonium chloride (1·5 g.) in water (10 c.c.) was hydrogenated (Raney nickel catalyst, 1·0 g.) at 60—65°/30 atm. for 4 hr. After cooling, the ammoniacal solution was evaporated under reduced pressure. The residual greenish-yellow gum (8·7 g.), which partly solidified, was stirred with water (100 c.c.), and the insoluble residue of amidoxime (3·4 g., 42%) was filtered off from the solution of the amidine hydrochloride. The amidine was isolated as its *toluene*-p-*sulphonate* which separated from ethanol–*iso*propanol in colourless needles, m. p. 168° (Found: C, 56·95; H, 5·05; N, 12·7. $C_{21}H_{23}O_3N_4ClS$ requires C, 56·4; H, 5·15; N, 12·5%). The *picrate* crystallised from ethanol in needles, m. p. 188° (Found: N, 19·6. $C_{20}H_{18}O_7N_7Cl$ requires N, 19·5%).

α-(N-*Benzyl*-N-2-*pyridylamino*)-NN′-*diphenylacetamidine*.—A mixture of 2-benzylaminopyridine (15·3 g.) and sodamide (3·3 g.) in benzene (100 c.c.) was heated under reflux with stirring for 1·5 hr., cooled, and treated with a solution of α-chloro-*NN*′-diphenylacetamidine (20·4 g.) in benzene (50 c.c.). The mixture was then refluxed for 2 hr., cooled, washed with dilute sodium hydroxide, dried ($MgSO_4$), and evaporated. The residue was stirred for 24 hr. with a little ethanol and filtered, giving α-(N-*benzyl*-N-2-*pyridylamino*)-NN′-*diphenylacetamidine* (3·3 g., 10%), which crystallised from ethanol–acetone (4 : 1) in prisms, m. p. 118—119° (Found: C, 79·2; H, 6·1; N, 14·4. $C_{26}H_{24}N_4$ requires C, 79·6; H, 6·2; N, 14·3%). The *monopicrate* separated from ethoxyethanol in stout needles, m. p. 192—192·5° (Found: N, 16·3. $C_{32}H_{27}O_7N_7$ requires N, 15·8%). The *dipicrate* separated from acetone in prisms, m. p. 150° (Found: C, 53·0; H, 3·4; N, 16·35. $C_{38}H_{30}O_{14}N_{10}$ requires C, 53·6; H, 3·6; N, 16·5%). The *sesquihydrochloride* separated from ethanol–ether in prisms, m. p. 199° (Found: N, 12·0; Cl′, 12·1. $C_{26}H_{24}N_4,1{\cdot}5HCl$ requires N, 12·5; Cl′, 11·9%).

Considerable decomposition occurred when the base (3·92 g.) was heated with ammonium benzenesulphonate (1·75 g.) and aniline (15 g.) at 100° for 2·5 hr. in a current of ammonia. No product could be isolated, the base being partly recovered as the monopicrate (1·5 g.), m. p. and mixed m. p. 192°.

Anhydro-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide* (VIII; R = Ac).—(a) *From* N-*benzyl*-N-2-*pyridylaminoacetaldoxime*. Acetic anhydride (200 c.c.) was added cautiously to the oxime (50 g.). When the initial reaction had subsided the solution was refluxed for 1·5 hr., cooled, poured on ice, and basified with an excess of 5N-sodium hydroxide with seeding. *Anhydro*-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (48 g., 77%) separated in pale brown rhombs as a *dihydrate* (Found: loss at 90°, 12·3. $C_{16}H_{15}ON_3,2H_2O$ requires H_2O, 12·0%). When dried to constant weight at 90°/5 mm., the rhombs changed to a yellow powder, m. p. 201° (decomp.) (Found: C, 72·9; H, 5·8; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%). The *toluene*-p-*sulphonate* separated from ethanol–ether in rhombs, m. p. 186° (Found: N, 9·5. $C_{23}H_{23}O_4N_3S$ requires N, 9·6%). The *picrate* separated from ethanol in needles, m. p. 147° (Found: N, 17·3. $C_{22}H_{18}O_8N_6$ requires N, 17·0%).

The oxime hydrochloride and acetic anhydride similarly gave a 90% yield of the same compound, m. p. 200° (decomp.).

(b) *From* N-*benzyl*-N-2-*pyridylaminoacetonitrile*. *N*-Benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride (5·84 g.) was acetylated by heating it on the steam-bath for 3 hours with acetic anhydride (21 c.c.). The anhydro-compound (5·66 g., 95%) was obtained as a yellow powder, m. p. 200° (decomp.).

When the nitrile itself was treated similarly, the anhydro-compound was obtained, after a tedious purification, in a yield of 58%, m. p. 193° (decomp.).

Pyrolysis of Anhydro-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Chloride*.—Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium hydroxide was converted into its gummy hydrochloride with hydrogen chloride (1 mol.) in absolute ethanol. This gum was heated at 180°/0·03 mm. for 5·5 hr. There was a yellow distillate which partly crystallised when kept, and benzyl chloride, recognised by its characteristic odour, was collected in a trap at −78°. Treatment of the yellow distillate with cold benzene gave 5-acetamidopyridino(1′ : 2′-1 : 2)-glyoxaline (0·28 g., 16%) as colourless needles, m. p. 155—176°, raised by recrystallisation from water to 196—197°, undepressed on admixture with a specimen, m. p. 198°, prepared by acetylation of 2-pyridylaminoacetonitrile.

α-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—Phenylacetaldehyde sodium hydrogen sulphite compound (47·5 g.) in water (70 c.c.) was heated with 2-aminopyridine (21 g.) at 95° for 4 hr. Sodium cyanide (42 g.) in water (150 c.c.) was added and the heating was continued for a further 1·5 hr.

The cooled solution was extracted with chloroform (3 × 200 c.c.), and the extract was dried ($MgSO_4$) and evaporated. The residue afforded *α-benzyl-N-2-pyridylaminoacetonitrile* (20 g., 38%) as buff needles (from ethyl acetate), m. p. 105·5° (Found: C, 75·3; H, 6·15; N, 18·8. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%). The *picrate* separated in needles, m. p. 205°, from ethoxyethanol (Found: N, 18·3. $C_{20}H_{16}O_7N_6$ requires N, 18·6%). The base and cold acetic anhydride–pyridine afforded *5-acetamido-4-benzylpyridino(1′ : 2′-1 : 2)glyoxaline* (70%) as colourless hydrated needles from 25% ethanol; after drying to constant weight at 56° the m. p. was 73—88°; when further heated the material resolidified and finally melted at 164° without any further loss in weight (Found: C, 71·9; H, 5·7; N, 15·7; active H, 0·68. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%; active H, 1·00). Recrystallisation regenerated the lower-melting form.

N-*Benzyl*-N-2-*pyridylethylenediamine*.—*N*-Benzyl-*N*-2-pyridylaminoacetonitrile (4·46 g.) was reduced with lithium aluminium hydride (0·76 g.) by the method of Amundsen and Nelson (*J. Amer. Chem. Soc.*, 1951, **73**, 242). **N-*Benzyl*-N-2-*pyridylethylenediamine*** (3·17 g., 70%) was obtained as a water-white oil, b. p. 152—155°/0·9 mm., n_D^{18} 1·6123 (Found: C, 74·3; H, 8·2; N, 18·5. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%). The *phthaloyl* derivative had m. p. 120°, undepressed on admixture with a specimen prepared from 2-benzylaminopyridine and 2-bromoethylphthalimide (Gardner and Stevens, *J. Amer. Chem. Soc.*, 1949, **71**, 1868, who record m. p. 121—122°) (Found: C, 73·55; H, 5·2; N, 11·9. Calc. for $C_{22}H_{19}O_2N_3$: C, 73·9; H, 5·35; N, 11·8%).

Acetylation of *N*-benzyl-*N*-2-pyridylethylenediamine (2·7 g.) with boiling acetic anhydride (10 c.c.) for 45 min. gave a mixture, separated by ethanol into the *diacetyl* derivative (1·9 g., 52%), prisms, m. p. 125° (Found: C, 69·8; H, 6·85; N, 13·8. $C_{18}H_{21}O_2N_3$ requires C, 69·4; H, 6·8; N, 13·5%), and the *monoacetyl* derivative (1·3 g., 40%), a yellow gum with green fluorescence, b. p. 220° (bath)/1·5 mm. (Found: C, 71·7; H, 7·1; N, 15·9. $C_{16}H_{19}ON_3$ requires C, 71·35; H, 7·1; N, 15·6%). Further acetylation of the monoacetate gave a mixture of mono- and di-acetates as before.

N-*Benzyl*-N′N′-*diethyl*-N-2-*pyridylethylenediamine*.—The reduction of *NN*-diacetyl-*N′*-benzyl-*N′*-2-pyridylethylenediamine (3·11 g.) with ethereal lithium aluminium hydride (0·76 g.) gave *N*-benzyl-*N′N′*-diethyl-*N*-2-pyridylethylenediamine (1·0 g., 35%) as an oil, b. p. 163°/1·2 mm., n_D^{21} 1·5715. The *oxalate* separated from ethanol in needles, m. p. 141° (Found: C, 64·3; H, 7·1; N, 11·2. $C_{20}H_{27}O_4N_3$ requires C, 64·3; H, 7·3; N, 11·3%), undepressed on admixture with the oxalate, m. p. 142°, prepared from the condensation product of 2-benzylaminopyridine and 2-diethylaminoethyl chloride (cf. Huttrer, Djerassi, Beears, Mayer, and Scholz, *ibid.*, 1946, **68**, 1999).

Hydrolysis of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium Hydroxide.—A solution of the anhydro-compound (2·0 g.) in 3N-hydrochloric acid (4·5 c.c.) was kept at room temperature for 4 days, then neutralised to pH 4·5 with 5N-sodium hydroxide with ice-cooling and treated with a warm concentrated solution of sodium toluene-*p*-sulphonate (2·0 g.). *N*-Benzyl-*N*-2-pyridylaminoacetonitrile toluene-*p*-sulphonate (1·46 g., 49%), m. p. 196—198°, was collected and recrystallised from 80% ethanol; it had m. p. and mixed m. p. 203—205°.

The anhydro-compound was not hydrolysed by (*a*) boiling ethanolic sodium ethoxide (81% recovery after 4 hr.), (*b*) boiling ethanol containing toluene-*p*-sulphonic acid (89% recovery after 1 hr.), or (*c*) aqueous-ethanolic sodium hydroxide (82% recovery after 13 days at room temperature).

When the anhydro-compound (5·0 g.) was hydrolysed with hot 6N-hydrochloric acid (10 c.c.) and then basified with 40% aqueous sodium hydroxide, sodium *N*-benzyl-*N*-2-pyridylaminoacetate (3·2 g., 73%) separated in needles, m. p. 294—297°, undepressed on admixture with the specimen prepared from *N*-benzyl-*N*-2-pyridylaminoacetonitrile (above). The benzylammonium salt separated from ethoxyethanol in prisms, m. p. 165° (medium rate of heating), undepressed on admixture with the specimen prepared from *N*-benzyl-*N*-2-pyridylaminoacetonitrile (Found: N, 11·7%).

Hydrogenation of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium Hydroxide.—The anhydro-compound (10·0 g.), dissolved in glacial acetic acid (100 c.c.), was hydrogenated with Adams platinum catalyst at 45—60° and atmospheric pressure. The hydrogen absorption was 97·5% of theory for 2 mols. The residue after filtration and evaporation below 30° was dissolved in 4N-sodium hydroxide (120 c.c.), and the solution was extracted with chloroform (3 × 130 c.c.). The dried ($MgSO_4$) extract was evaporated and the solid residue was crystallised by dissolving it in 80% acetone (23 c.c.) and adding acetone (42 c.c.). The *tetrahydro*-derivative (7·8 g., 68%) separated in rhombs as a dihydrate, m. p. 274—275° (Found: loss at 100°, 12·0.

$C_{16}H_{19}ON_3,2H_2O$ requires H_2O, 11·8%. Found, on material dried at 100°: C, 70·9; H, 7·1; N, 15·5. $C_{16}H_{19}ON_3$ requires C, 71·3; H, 7·1; N, 15·6%).

After hot acid hydrolysis a product was obtained as a *picrate* (91% yield), m. p. 152·5—153°. On recrystallisation from ethanol it separated in dendrites, m. p. 153·5° (Found: C, 52·45; H, 3·9; N, 15·4. $C_{20}H_{19}O_8N_5$ requires C, 52·5; H, 4·2; N, 15·3%). A quantitative experiment showed the liberation of acetic acid (1·00 mol.) and ammonia (1·01 mol.). The base could not be crystallised, and it did not react with hydroxylamine, semicarbazide, or 2 : 4-dinitrophenylhydrazine. It was soluble in water and gave a non-crystalline, water-insoluble benzoate.

Alkylation of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—The anhydro-compound (7·95 g.), suspended in acetone (50 c.c.), was heated under reflux for 50 min. with methyl iodide (3·6 c.c.). *5-Acetmethylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium iodide* (10·6 g., 86%), m. p. 193°, was collected and recrystallised from ethanol–ether, separating in colourless plates, m. p. 194° (Found: C, 50·3; H, 4·3; N, 10·5; I′, 31·4; OMe, 1·35. $C_{17}H_{18}ON_3I$ requires C, 50·1; H, 4·45; N, 10·3; I′, 31·2; OMe, 0 or 7·6%).

A hot acid hydrolysate was basified and distilled into 0·1N-hydrochloric acid. Evaporation gave a 94% yield of methylammonium chloride, m. p. 214—220° after crystallisation from *iso*propanol, undepressed on admixture with an authentic specimen (Found: Cl′, 52·2, 55·4. Calc. for CH_6NCl: Cl′, 52·7%). This was converted into methylammonium picrate, m. p. and mixed m. p. 206—207° (decomp.).

A solution of the iodide (1·02 g.) in a mixture of 0·5N-hydrochloric acid (5 c.c.) and ethanol (2·5 c.c.) deposited a mixture of yellow needles and purple prisms after 4 weeks at room temperature. The solid was collected and extracted with cold methanol (5 c.c.); on the addition of ether *3-benzyl-5-methylaminopyridino*(1′ : 2′-1 : 2)*glyoxalinium iodide* (0·28 g., 31%) separated in yellow needles, m. p. 156° (Found: C, 49·1; H, 4·4; N, 11·7; I′, 34·1. $C_{15}H_{16}N_3I$ requires C, 49·3; H, 4·4; N, 11·5; I′, 34·8%). The residual purple prisms, m. p. 119° (0·20 g.) after recrystallisation from methanol, were not investigated further. Methylamine, identified as its hydrochloride (35 mg.) and picrate, was isolated from the aqueous hydrolysate in a parallel experiment after only 2 days.

When the anhydro-compound (2·65 g.) was treated with methyl iodide (1·6 g.) in methanol (10 c.c.) at room temperature for 4 weeks, the methylamino-derivative (2·38 g., 65%) separated in salmon-pink needles, m. p. 143—145°. Crystallisation from methanol–ether with charcoal gave yellow needles, m. p. 156°, undepressed on admixture with the product obtained above.

A mixture of the anhydro-compound (3·96 g.), ethyl iodide (3·0 g.), and acetone (30 c.c.) was heated under reflux for 3 hr., cooled, and seeded. The crude *5-acetethylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium iodide* crystallised from ethanol–ether in rhombs, m. p. 185° (Found: N, 10·2. $C_{18}H_{20}ON_3I$ requires N, 10·0%).

The anhydro-compound reacted completely in about 5 min. with allyl iodide in acetone. *5-Acetallylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium reineckate* separated from acetone–ethanol as a microcrystalline powder, m. p. 158—160° (Found: C, 44·2; H, 4·5; N, 19·7. $C_{23}H_{26}ON_9S_4Cr$ requires C, 44·2; H, 4·2; N, 20·2%).

When the anhydro-compound was treated with *n*-propyl toluene-*p*-sulphonate in hot *iso*butyl methyl ketone for 15 min. *5-acetpropylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium toluene*-p-*sulphonate* (60%) was obtained, separating from ethanol–ether in needles, m. p. 147·5° (Found: C, 64·4; H, 6·1; N, 9·0. $C_{26}H_{29}O_4N_3S$ requires C, 65·1; H, 6·1; N, 8·8%).

Anhydro-5-acetamido-3-benzyl-3′-methylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—This compound was obtained by the acetal–oxime route used for the preparation of (VIII; R = Ac). Condensation of 2-benzylamino-1 : 1-dimethoxyethane and 2-bromo-3-methylpyridine (Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574) afforded 2-[*N-benzyl*-N-(*3-methyl-2-pyridyl*)*amino*]-1 : 1-*dimethoxyethane* (56%), b. p. 140—144°/0·25 mm., n_D^{22} 1·5583 (Found: N, 9·7. $C_{17}H_{22}O_2N_2$ requires N, 9·7%). Hydrolysis and oximation afforded a non-crystalline oxime which with acetic anhydride gave *anhydro-5-acetamido-3-benzyl-3′-methylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (15%) as a *monohydrate*, red-brown rhombs, m. p. 245—247° (decomp.) (from water) (Found: H_2O, 6·1. $C_{17}H_{17}ON_3,H_2O$ requires H_2O, 6·1%). On drying at 100° the colour changed to yellowish green and the m. p. rose to 249—250° (decomp.) (Found: C, 73·2; H, 6·0; N, 14·95. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·05%).

Anhydro-5-acetamido-3-(2 : 4 : 6-*trimethylbenzyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Similarly, 1 : 1-dimethoxy-2-(2 : 4 : 6-trimethylbenzylamino)ethane, b. p. 125—132°/0·9 mm. (35% yield from the condensation of 2 : 4 : 6-trimethylbenzylamine and 2-bromo-1 : 1-dimethoxyethane) afforded, successively, 2-[*N*-2-pyridyl-*N*-(2 : 4 : 6-trimethylbenzyl)amino]-

1 : 1-dimethoxyethane (61%; b. p. 174—176°/0·8 mm.), **N-2-*pyridyl*-N-(2 : 4 : 6-*trimethylbenzyl*)*aminoacetaldoxime*** (41%), needles (from ethanol), m. p. 172° (Found: C, 72·3; H, 7·1; N, 14·45. $C_{17}H_{21}ON_3$ requires C, 72·1; H, 7·5; N, 14·8%) [*hydrochloride*, plates (from water), m. p. 222—223° (Found: Cl′, 10·9. $C_{17}H_{21}ON_3$,HCl requires Cl′, 11·1%)], and ***anhydro*-5-*acetamido*-3-(2 : 4 : 6-*trimethylbenzyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide*** (30%), which crystallised from water as colourless, hydrated needles, m. p. 210° (decomp.), which became yellow when dried at 100° (Found: C, 73·7; H, 6·8; N, 14·0. $C_{19}H_{21}ON_3$ requires C, 74·2; H, 6·9; N, 13·7%).

Anhydro*-5-*acetamido*-3-(2-*thienylmethyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide*.**—1 : 1-Dimethoxy-2-(2-pyridylamino)ethane, sodamide, and 2-thienylmethyl chloride in toluene gave **1 : 1-*dimethoxy*-2-(N-2-*pyridyl*-N-2′-*thienylmethyl*)*ethane (61%), b. p. 166—173°/1 mm. (Found: C, 59·9; H, 6·2; N, 10·0. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5; N, 10·1%). Hydrolysis and oximation yielded **N-2-*pyridyl*-N-(2-*thienylmethyl*)*aminoacetaldoxime*** (62%), plates (from ethanol), m. p. 106° (Found: C, 58·2; H, 5·4; N, 16·4. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3; N, 17·0%). Boiling acetic anhydride afforded ***anhydro*-5-*acetamido*-3-(2-*thienylmethyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide*** (74%) as colourless, hydrated plates (from water), m. p. 93° (Found: loss at 78°, 11·7. $C_{14}H_{13}ON_3S,2H_2O$ requires H_2O, 11·7%). The dried product was a yellow powder, m. p. 185—186° (decomp.) (Found: C, 61·5; H, 4·9; N, 15·5. $C_{14}H_{13}ON_3S$ requires C, 62·0; H, 4·8; N, 15·5%). The *picrate* separated from ethanol in stout needles, m. p. 149—150° (Found: C, 48·5; H, 3·4; N, 16·6. $C_{20}H_{16}O_8N_6S$ requires C, 48·0; H, 3·2; N, 16·8%).

Anhydro*-5-*acetamido*-3-*ethylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide*.**—A mixture of 2-pyridylaminoacetonitrile (10·0 g.), ethyl iodide (11·9 g.), and chloroform (40 c.c.) was heated under reflux for 24 hr. and poured into ether (200 c.c.). The resulting **N-*ethyl*-N-2-*pyridyl*-*aminoacetonitrile hydriodide (11·8 g., 54%) separated from ethanol in prisms, m. p. 182° (Found: C, 37·85; H, 4·15; N, 14·5; I′, 43·8. $C_9H_{12}N_3I$ requires C, 37·4; H, 4·2; N, 14·5; I′, 43·9%). Boiling the finely powdered material with acetic anhydride for 10 min. yielded ***anhydro*-5-*acetamido*-3-*ethylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide trihydrate*** as colourless needles (from water), m. p. 92° (Found: loss at 65°, 21·2. $C_{11}H_{13}ON_3,3H_2O$ requires H_2O, 21·0%). The yellow anhydrous ***base*** had m. p. 163° (decomp.) (Found: N, 20·4. $C_{11}H_{13}ON_3$ requires N, 20·7%). The hydriodide separated from ethanol in rhombs, m. p. 248°.

Anhydro*-5-*acetamido*-3-*phenylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide*.**—2-Anilinopyridine, sodamide, and 2-bromo-1 : 1-dimethoxyethane in benzene gave **1 : 1-dimethoxy-2-(*N*-phenyl-*N*-2-pyridylamino)ethane** (19%), b. p. 140—145°/1·2 mm.; 2-anilinopyridine (47%) was recovered. Hydrolysis and oximation gave **N-*phenyl*-N-2-*pyridylaminoacetaldoxime (45%), prisms (from ethanol), m. p. 93° (Found: C, 69·3; H, 5·95; N, 18·2. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·8; N, 18·5%). Boiling acetic anhydride afforded ***anhydro*-5-*acetamido*-3-*phenylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide*** (69%) as pale brown hydrated needles from water. The anhydrous form was obtained as a yellow powder, m. p. 193° (Found: C, 71·15; H, 5·3; N, 16·8. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

Anhydro*-5-*acetamido*-3-(2-*pyridyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide*.**—**2-(*Di*-2-*pyridyl*)*amino*-1 : 1-*dimethoxyethane (34%) was prepared from 1 : 1-dimethoxy-2-(2-pyridylamino)ethane (Kaye, *loc. cit.*), sodamide, and 2-bromopyridine and had b. p. 155—160°/1 mm. (Found: C, 65·3; H, 6·8; N, 16·3. $C_{14}H_{17}O_2N_3$ requires C, 64·8; H, 6·6; N, 16·2%). It was also prepared in 25% yield from 2 : 2′-dipyridylamine, sodamide, and 2-bromo-1 : 1-dimethoxyethane. Hydrolysis and oximation gave crude *NN*-di-2-pyridylaminoacetaldoxime (36%) as an oil. Boiling acetic anhydride converted this into a water-soluble product which could be extracted from alkaline solution with chloroform. Addition of light petroleum to the chloroform extract afforded ***anhydro*-5-*acetamido*-3-(2-*pyridyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide*** (17%) as needles, m. p. 210—212° (decomp.) with rapid heating (Found, on material dried at 100°: C, 66·5; H, 5·0; N, 21·9. $C_{14}H_{12}ON_4$ requires C, 66·65; H, 4·8; N, 22·2%). The crystals were variably solvated, depending on the relative proportions of chloroform and light petroleum in the solvent.

Anhydro*-3-*benzyl*-5-*propionamidopyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide*.**—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride (3 g.) under reflux with propionic anhydride (10 c.c.) for 45 min. gave ***anhydro*-3-*benzyl*-5-*propionamidopyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide monohydrate (3·1 g., 90%) as needles (from water), m. p. 135—136° (Found, on material dried at 78°: C, 69·2; H, 6·4; N, 14·3; H_2O, 5·5. $C_{17}H_{17}ON_3,H_2O$ requires C, 68·7; H, 6·4; N, 14·1; H_2O, 6·05%). Heating an acetone solution of this hydrate with methyl iodide under reflux for 15 min. gave *3-benzyl-5-propionmethylamidopyridino*(1′ : 2′-1 : 2)-

glyoxalinium iodide (65%) as prisms (from ethanol–ether), m. p. 135° (Found: N, 10·1. $C_{18}H_{20}ON_3I$ requires N, 10·0%).

Anhydro-5-benzamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride with benzoyl chloride in pyridine for 2 hr. at 95° afforded *anhydro-5-benzamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (1·7 g., 33%) as solvated yellow-brown prisms, m. p. 188°, from chloroform–light petroleum (b. p. 60—80°) (Found: loss at 100°, 26·6. $C_{21}H_{17}ON_3,CHCl_3$ requires $CHCl_3$, 26·7%. Found, on material dried at 100°: C, 77·0; H, 4·9; N, 13·1. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2; N, 12·8%). When the oxime was substituted for the nitrile hydrochloride the yield was only 14%.

Anhydro-5-benzenesulphonamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride with benzenesulphonyl chloride in pyridine for 2 hr. at 95° yielded *anhydro-5-benzenesulphonamido-3-benzylpyridino*(1′ : 2′-1 : 2)-*glyoxalinium hydroxide* (64%), green needles (from methanol), m. p. 208° (Found: N, 11·7. $C_{20}H_{17}O_2N_3S$ requires N, 11·6%). Heating under reflux with ethanolic methyl iodide for 10 hr. yielded *5-benzenesulphonmethylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium iodide* (79%), plates (from water), m. p. 201° (Found: C, 48·95; H, 4·0; N, 8·3. $C_{21}H_{20}O_2N_3IS$ requires C, 49·9; H, 4·0; N, 8·3%).

1-*Carbamoylmethyl*-1 : 2-*dihydro*-2-*sulphanilimidopyridine* (X; R = NH_2, R′ = $CO{\cdot}NH_2$).—Chloroacetamide (10·0 g.) was added to a filtered solution of sulphapyridine (24·9 g.) in N-sodium hydroxide (100 c.c.), and the mixture was heated for 2 hr. at 95°. After cooling, the product was collected and washed with 4% sodium hydroxide solution, giving 1-*carbamoylmethyl*-1 : 2-*dihydro*-2-*sulphanilimidopyridine* (19·0 g., 62%) as minute prisms, m. p. 208—210° (decomp.) (Found: N, 18·3. $C_{13}H_{14}O_3N_4S$ requires N, 18·3%). Sulphapyridine (3·8 g., 15%; m. p. 186—187°) was recovered.

4-*Hydroxypyridino*(1′ : 2′-1 : 2)*glyoxaline* (XI).—1-Carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine (9·5 g.) was heated with N-sodium hydroxide (40 c.c.) for 2·5 hr. at 95°. The clear, cooled solution was neutralised with N-hydrochloric acid (40 c.c.). The precipitated 1-carboxymethyl-1 : 2-dihydro-2-sulphanilimidopyridine [8·0 g., 84%; m. p. 127—157° (decomp.)] solidified on being seeded. The *anilinium* salt separated from water in clusters of prisms, m. p. 115° (Found: N, 13·8. $C_{19}H_{20}O_4N_4S$ requires N, 14·0%). The acid was heated under reflux with 5N-hydrochloric acid (50 c.c.) for 18 hr., then cooled. Sulphanilic acid (2·7 g., 60%) separated and was characterised by conversion into 2 : 4 : 6-tribromoaniline, m. p. and mixed m. p. 120°. The filtered solution was evaporated to dryness *in vacuo* and the residue was dissolved in water. Excess of aqueous lithium picrate precipitated 4-hydroxypyridino(1′ : 2′-1 : 2)glyoxalinium picrate (8·1 g., 86%) as needles, m. p. 208° (decomp.), undepressed on admixture with a specimen prepared by Reindel's method (*loc. cit.*) (Found: C, 43·2; H, 2·5; N, 18·9. Calc. for $C_{13}H_9O_8N_5$: C, 43·0; H, 2·5; N, 19·3%).

1-*Cyanomethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine.*—Condensation of chloroacetonitrile and 2-toluene-*p*-sulphonamidopyridine similarly afforded 1-*cyanomethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine* (67%) which separated from ethanol in rhombs, m. p. 160—162° (Found: N, 14·5. $C_{14}H_{13}O_2N_3S$ requires N, 14·6%).

1-*Carbamoylmethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine.*—Prepared by the method used for the sulphanilyl analogue, this *amide* (70%) separated from 50% ethoxyethanol in plates, m. p. 166—173° (Found: N, 13·6. $C_{14}H_{15}O_3N_3S$ requires N, 13·8%); 2-toluene-*p*-sulphonamidopyridine (24%) was recovered, m. p. 213°. Hydrolysis in hot N-sodium hydroxide yielded 1-*carboxymethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine* (95%), thick plates, m. p. 190°, from ethanol–ether (Found: C, 55·1; H, 4·45; N, 9·1. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·1%). The *benzylammonium* salt crystallised from ethanol in plates, m. p. 173° (Found: N, 10·1. $C_{21}H_{23}O_4N_3S$ requires N, 10·2%).

4-*Acetamidopyridino*(1′ : 2′-1 : 2)*glyoxaline.*—1-Carbamoylmethyl-1 : 2-dihydro-2-toluene-*p*-sulphonimidopyridine (5·0 g.) was heated under reflux with acetic anhydride (15 c.c.) for 50 min. After evaporation of the solution under reduced pressure, the residue was dissolved in a little ethanol and basified with ice-cooling. 4-*Acetamidopyridino*(1′ : 2′-1 : 2)*glyoxaline* (1·0 g., 35%) was collected and recrystallised from ethanol or ethoxyethanol, from which it separated in long needles, m. p. 229° (Found: C, 61·5; H, 5·1; N, 23·6. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0%).

Similar acetylation of 1-carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine gave the same compound (36%), m. p. 230°, undepressed by the specimen prepared above.

Hydrolysis with hot 30% sodium hydroxide solution afforded 4-aminopyridino(1′ : 2′-1 : 2)-glyoxaline (58%) as a crude solid, m. p. 73—83° after rapid distillation at 2 mm. (some decomp.),

unstable in air. The *picrate* separated from 50% ethanol in clusters of brown needles, m. p. 200° (decomp.) (Found: C, 43·2; H, 2·9; N, 23·6. $C_{13}H_{10}O_7N_6$ requires C, 43·1; H, 2·8; N, 23·2%)

The authors are indebted to Dr. J. D. S. Goulden and Mr. P. G. Marshall for the determination of infra-red spectra.

RESEARCH LABORATORIES, BOOTS PURE DRUG CO., LTD.,
NOTTINGHAM.

[*Received, October 24th,* 1953.]

Kinetics of the Decomposition of Tetralin Hydroperoxide in Acidic and Basic Solvents.

By (MISS) J. E. HAY, (MISS) N. M. JOHNSTONE, C. F. H. TIPPER, and R. K. WILLIAMS.

[Reprint Order No. 4614.]

The kinetics of the decomposition of tetralin hydroperoxide have been investigated under conditions which should favour heterolytic fission of the hydroperoxide molecules. The overall decomposition was of the first order at concentrations below 0·2M, and k did not depend on the initial concentration. Addition of water increased the rate of reaction in acetic acid and also the overall activation energy. Probably the water tended to suppress a chain reaction occurring in the dry acid. The decomposition was subject to acid catalysis in chlorobenzene solution. Addition of small amounts of sodium hydroxide greatly increased the rate of decomposition in ethylene glycol–water mixture (24 : 1; by vol.), and reduced the overall activation energy from 24·8 to 19·4 kcal. Reaction schemes involving ions are suggested.

With nitrobenzene and pyridine as solvents, however, the decomposition probably does not involve ions.

THE decomposition of tetralin hydroperoxide has been investigated by a number of workers (see Robertson and Waters, *J.*, 1948, 1578, for references). The solvents used were nearly all neutral organic compounds of low dielectric constant. Robertson and Waters (*loc. cit.*), who studied both the kinetics and the products, concluded that in such solvents the decomposition occurred by two simultaneous mechanisms: a molecular re-arrangement, and a split into free radicals followed by an induced chain reaction probably involving solvent radicals. It was suggested, however, that ionic decomposition could occur, especially in the presence of acids. Recently Kharasch and Burt (*J. Org. Chem.*, 1951, **16**, 150) and Kharasch, Fono, Nudenberg, and Bischoff (*ibid.*, 1952, **17**, 207) have investigated the products formed when tetralin hydroperoxide was decomposed in acid or alkaline solution, and have proposed reaction mechanisms involving ionic intermediates. As a complement to this work the kinetics of the decomposition (in an inert atmosphere) under acidic and basic conditions have been studied, iodometric titration or a colorimetric method being used to determine the hydroperoxide.

The plots of log [hydroperoxide] against time were straight lines, up to 75—95% decomposition (as far as the reaction was followed), under nearly all conditions. Fig. 1 shows a selection of the results. The velocity constants were reproducible to within 5%, different samples of hydroperoxide or solvent being used. The initial concentration of hydroperoxide varied but was always less than 0·3M.

As a preliminary, the decomposition in nitrobenzene, a neutral solvent of high dielectric constant, was studied. The rate of reaction became appreciable above 130°, k being 1·40, 2·57, and 9·43 $\times$ 10^{-3} min.$^{-1}$ at 131·2°, 139·6°, and 153·0°, respectively, and an initial concentration of 0·12M. The overall activation energies, calculated for the lower and the higher temperature range, were 24·1 and 33·6 kcal., respectively, as compared with 24·4 kcal. for the decomposition in tetralin (Robertson and Waters, *loc cit.*). The difference is well outside the experimental error and the explanation is not apparent. The % of decomposition in one hour at 116°, calculated by using the lower value of the activation energy, was

3·0%, less than that found by Robertson and Waters (*loc. cit.*) with chlorobenzene as solvent at the same temperature. Thus it seems unlikely that any appreciable ionic decomposition was occurring in nitrobenzene, and no further experiments were performed.

The effect of addition of water on the decomposition in acetic acid is shown in Fig. 2. The use of distilled or undistilled "AnalaR" glacial acetic acid gave identical results, within the experimental error. Addition of up to 5 mole % of water had little effect, but further addition up to about 45—50 mole % greatly increased the rate of decomposition. Still further increase in the water content had no further effect. Change in the initial hydroperoxide concentration from 0·06 to 0·3M caused less than 5% change in the first-order rate

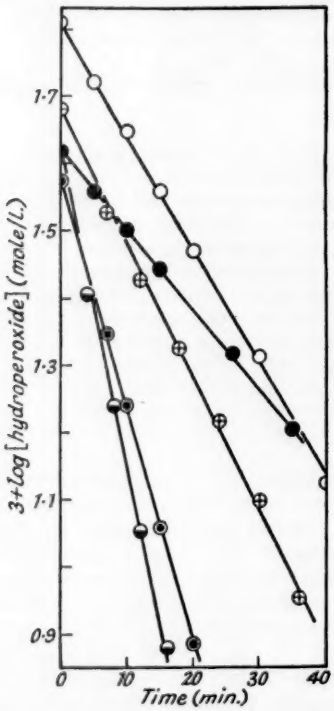


FIG. 1. *Decomposition of tetralin hydroperoxide in various solvents. Nitrogen was passed through the solution.*

○ Solvent, acetic acid + 3·2 mole % of water. Temp. = 114·4°. Initial concn. = 0·065M.

⊕ Solvent, ethylene glycol–water (24 : 1) + 0·02 mole/l. of NaOH. Temp. = 77·7°. Initial concn. = 0·048M.

● Solvent, ethylene glycol–water (24 : 1). Temp. = 114·9°. Initial concn. = 0·042M.

◒ Ordinate + 0·2. Solvent, acetic acid + 67·9 mole % of water. Temp. = 98·9°. Initial concn. = 0·069M.

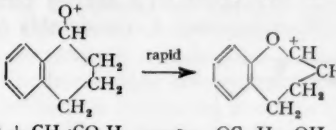
◉ Ordinate − 1·1. Solvent, chlorobenzene + 0·35M-monochloroacetic acid. Temp. = 115·9°. Initial concn. = 0·003M.

constant in aqueous acid containing 3·2 or 67·9 mole % of water, and thus at these relatively low concentrations the decomposition is of the first order. The overall activation energies of decomposition in these two aqueous acids were 18·4 and 20·7 kcal./mole, and the temperature-independent factors were $1·3 \times 10^7$ and $3·1 \times 10^9$ sec.$^{-1}$, respectively (Fig. 3). The addition of 0·76 mole/l. of acrylonitrile to these two solvents caused no appreciable change in the rate of decomposition (Fig. 3), and only small amounts of polymer were formed (0·194 or 0·002 g., severally) during the complete reaction of 20 ml. of 0·06M-hydroperoxide solution in acetic acid containing 3·2 or 67·9 moles % of added water and 10 vol. % of added acrylonitrile.

The results show that little free-radical decomposition occurred, and they are similar to those obtained from a study of the decomposition of decalin hydroperoxide in aqueous acetic acid (Tipper, *J.*, 1953, 1675). Probably the explanation of the increase in overall activation energy as well as of k as the water content was increased is again that addition of water suppressed an induced ionic chain decomposition. Kharasch and Burt (*loc. cit.*) found that the main product of the decomposition of tetralin hydroperoxide in glacial acetic acid containing 0·1 mole % of perchloric acid was the aldol of γ-(*o*-hydroxyphenyl)butyraldehyde, and Kharasch, Fono, Nudenberg, and Bischoff (*loc. cit.*) state that in dilute solution

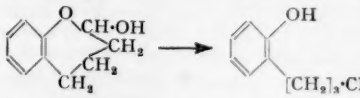
the reaction was of the first order at 25°. The following simple scheme, which is an adaptation of that proposed by Kharasch and Burt (*loc. cit.*), explains the results quite reasonably.

$$C_{10}H_{11}\cdot O\cdot OH + H^+ \longrightarrow C_{10}H_{11}O^+ + H_2O \quad . . . . . (1)$$



$$OC_{10}H_{11}^+ + CH_3\cdot CO_2H \longrightarrow OC_{10}H_{11}\cdot OH + CH_3\cdot CO^+ * \quad . . . . . (3)$$

$$CH_3\cdot CO^+ + C_{10}H_{11}\cdot O\cdot OH \longrightarrow C_{10}H_{11}O^+ + CH_3\cdot CO_2H \quad . . . . . (4)$$



$$\left.\begin{array}{ll} & OC_{10}H_{11}^+ + CH_3\cdot CO^+ \longrightarrow \\ \text{or} & OC_{10}H_{11}^+ + C_{10}H_{11}\cdot O\cdot OH \longrightarrow \\ \text{or} & CH_3\cdot CO^+ + C_{10}H_{11}\cdot O\cdot OH \longrightarrow \end{array}\right\} \text{inert products} \quad . . . . . \left\{\begin{array}{l}(6a)\\(6b)\\(6c)\end{array}\right.$$

* The $CH_3\cdot CO^+$ ion, once formed, might exist in acetic acid through successive regeneration reactions:

$$CH_3\cdot CO^+ + CH_3\cdot CO_2H = CH_3\cdot CO_2H + CH_3\cdot CO^+$$

It being assumed that the concentrations of the $OC_{10}H_{11}^+$ and $CH_3\cdot CO^+$ ions were stationary and that the hydrogen-ion concentration was constant, it can be shown that the scheme with equation (6*a*), (6*b*), or (6*c*) as the termination reaction yields a first-order rate expression for the decomposition. The justification for any of the three termination reactions can only be that the correct rate expression is obtained since any products postulated will merely be speculative. Reactions (6*b*) and (6*c*) are perhaps more likely than (6*a*) since the last involves the reaction of similarly charged ions. With higher initial concentrations of the hydroperoxide, reaction of some $OC_{10}H_{11}^+$ ions with undecomposed molecules (7) would be expected to occur as postulated by Kharasch and Burt (*loc. cit.*). This would cause

$$OC_{10}H_{11}^+ + C_{10}H_{11}\cdot O\cdot OH = OC_{10}H_{11}\cdot OH + C_{10}H_{11}O^+ \quad . . . . . (7)$$

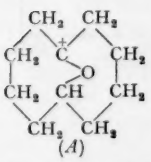
deviation from first order and Kharasch, Fono, Nudenberg, and Bischoff (*loc. cit.*) in fact state that the decomposition of concentrated solutions in acetic acid at 25°, catalysed by perchloric acid, is of the second order. As water was added to the acetic acid reaction (3) was probably progressively replaced by

$$CH_3\cdot CO^+ + H_2O = CH_3\cdot CO_2H + H^+ \quad . . . . . (8a)$$

$$OC_{10}H_{11}^+ + H_2O = OC_{10}H_{11}\cdot OH + H^+ \quad . . . . . (8b)$$

leading to the elimination of the chain reaction [cf. Tipper, *loc cit.*, reaction (8)].

A detailed mechanism for the ionic chain decomposition of decalin hydroperoxide in dry acetic acid was not proposed previously (Tipper, *loc. cit.*), but it is quite likely that one exactly similar to the above [excluding reaction (5)] occurred, *A* being the active carbonium ion. If this were so, then the reaction analogous to (7) must have occurred even at fairly low concentrations since the overall order of the decomposition was greater than unity except with very dilute solutions.


(*A*)

The first-order decomposition of tetralin hydroperoxide in chlorobenzene [an average of 13% decomposition in 1 hour at 116° as compared with 10% decomposition reported by Robertson and Waters (*loc. cit.*)] was catalysed by small amounts of acetic acid. The degree of catalysis at 117·3° did not depend on the concentration of acid (up to 0·7M) within the experimental error, in contrast with the results with decalin hydroperoxide, but increased with increasing initial hydroperoxide concentration ($k_{cat.}$ = 0·0536 min.$^{-1}$ with 0·05M-hydroperoxide and 0·00567 min.$^{-1}$ with 0·0031M). The overall activation energy of the catalysed part of the decomposition was very roughly 19 kcal./mole ($k_{cat.}$ = 0·00355 min.$^{-1}$ at 110·1° and 0·0031M-hydroperoxide). Mono-, di-, and tri-chloroacetic acid were increasingly powerful catalysts, but, since in these cases the rate appeared to depend on the acid

concentration, nothing quantitative can be deduced. However the results are in general accord with theoretical expectation.

The decomposition in pyridine at 80—100° was very rapid for the first few minutes and then became slower, and the plot of log of concentration against time became straight. However doubling the initial concentration increased k considerably (k = 0·00357 min.$^{-1}$ with 0·05M and 0·00500 min.$^{-1}$ with 0·10M at 98·9°). The initial rapid decomposition was probably due to traces of impurities, produced by a very small amount of oxidation of the redistilled solvent, since, on leaving this overnight in the presence of air, the initial decomposition was greatly prolonged. The overall activation energy of the uncatalysed decomposition was about 23·5 kcal./mole (k = 0·000560 min.$^{-1}$ at 79·2° and 0·05M initial concentration), and probably the high rate (55% decomposition in 1 hour at 116°) and variation of

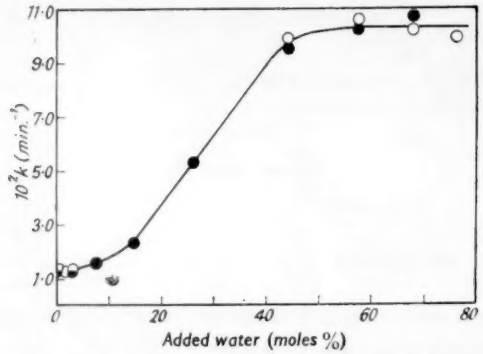
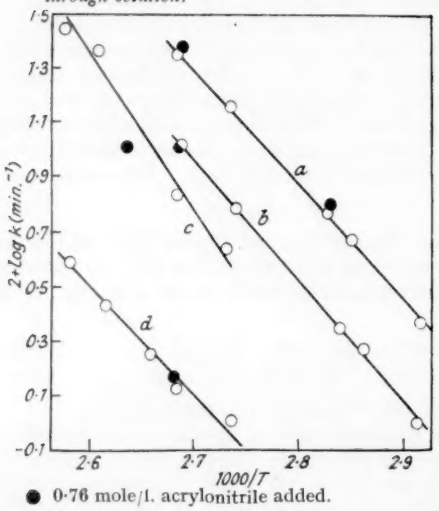


FIG. 2. *Effect of water on the rate of decomposition of tetralin hydroperoxide in acetic acid. Temp.* = 99·5°. *Initial concn.* = 0·122M. *Nitrogen passed through solution.*

● Undistilled "AnalaR" acetic acid.
○ Distilled acid.

FIG. 3. *Effect of temperature on the decomposition of tetralin hydroperoxide. Nitrogen passed through solution.*



● 0·76 mole/l. acrylonitrile added.

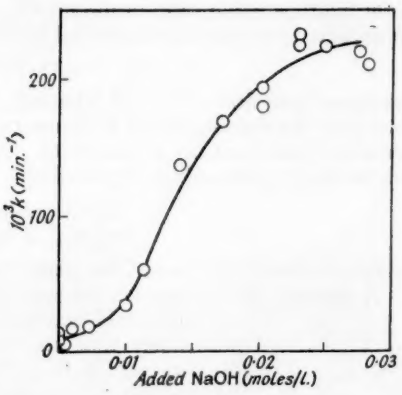
a, Solvent, 24/1 ethylene glycol–water mixture + 0·02 mole/l. NaOH. Initial concn. = 0·049M.

b, Solvent, acetic acid + 67·9 mole % of water. Initial concn. = 0·061M.

c, Solvent, 24 : 1 ethylene glycol–water mixture. Initial concn. = 0·049M.

d, Solvent, acetic acid + 3·2 mole % of water. Initial concn. = 0·061M.

FIG. 4. *Effect of sodium hydroxide on the decomposition of tetralin hydroxide in ethylene glycol–water* (24 : 1 *by vol.*). *Temp.* = 99·0°. *Initial concn.* = 0·049M. *Nitrogen passed through solution.*



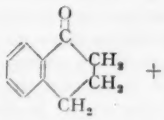
k with initial concentration were due to a rapid free-radical chain reaction as with decalin hydroperoxide.

In contrast to the results with decalin hydroperoxide, addition of small amounts of sodium hydroxide to a solution of tetralin hydroperoxide in ethylene glycol–water (4 vol. % of H_2O) at 100° caused a very considerable increase in the rate of decomposition (Fig. 4). The velocity constant remained unchanged, within the experimental error, over the range of initial hydroperoxide concentration 0·0375—0·113M, for the decomposition with or without added sodium hydroxide, and thus the reaction is of the first order at least under these conditions. The overall activation energies of decomposition without alkali and with 0·02 mole/l. of sodium hydroxide were 24·8 and 19·4 kcal./mole, respectively (Fig. 3). Addition of 0·76 mole/l. of acrylonitrile retarded the reaction in the neutral alcohol–water mixture (Fig. 3) and 1·29 g. of polymer were formed during the complete reaction of 25 ml. of 0·05M-hydroperoxide solution containing 8 vol. % of the monomer. Probably a free-radical chain reaction was occurring. However, in the presence of 0·02 mole/l. of sodium hydroxide, acrylonitrile caused no retardation (Fig. 3), and no polymer was precipitated. Obviously no free radicals were present during the decomposition in an alkaline medium.

It has been known for some time that aqueous sodium hydroxide decomposes tetralin hydroperoxide, and Kharasch, Fono, Nudenberg, and Bischoff (*loc. cit.*) found that in concentrated alkali the rate was rapid at 25°. Water, tetralone, and higher oxidation products were formed by using *tert.*-butyl alcohol as the solvent. Probably the $C_{10}H_{11}O{\cdot}O^-$ ion was formed in the initial step:

$$C_{10}H_{11}{\cdot}O{\cdot}OH + OH^- \longrightarrow C_{10}H_{11}O{\cdot}O^- + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

followed by

$$C_{10}H_{11}O{\cdot}O^- \longrightarrow$$  $$+ OH^- * \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

or if an induced chain decomposition was occurring then the following reactions might possibly have been in competition with (10).

$$C_{10}H_{11}O{\cdot}O^- + \begin{matrix}CH_2{\cdot}OH\\ CH_2{\cdot}OH\end{matrix} \longrightarrow C_{10}H_{10}O + \begin{matrix}CH_2O^-\\ CH_2{\cdot}OH\end{matrix} + H_2O \quad . \quad . \quad . \quad . \quad (11)$$

$$\begin{matrix}CH_2{\cdot}O^-\\ CH_2{\cdot}OH\end{matrix} + C_{10}H_{11}{\cdot}O{\cdot}OH \longrightarrow \begin{matrix}CH_2{\cdot}OH\\ CH_2{\cdot}OH\end{matrix} + C_{10}H_{11}O{\cdot}O^- \quad . \quad . \quad . \quad . \quad . \quad (12)$$

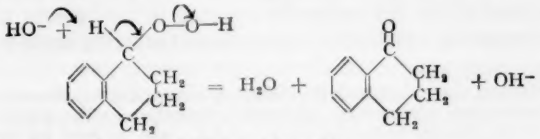
Thus it is probably not permissible to associate the activation energy of 19·4 kcal. with reaction (9).

Experimental

The kinetics of the decomposition were studied as described previously (Tipper, *J.*, 1952, 2966). The hydroperoxide was determined by the iodometric method of Wagner, Smith, and Peters (*Ind. Eng. Chem. Anal.*, 1947, **19**, 976) or by the ferrous thiocyanate method (Tipper, *loc. cit.*).

Tetralin hydroperoxide was prepared by the oxidation of tetralin for 12—18 hr. at 100°. Unchanged hydrocarbon was distilled off, the syrup remaining was left in the refrigerator for several days, and the solid was then filtered off. The crude hydroperoxide was recrystallised at least three times from light petroleum (b. p. 40—60°). The final product melted at 55°, and released 97—99% of the theoretical quantity of iodine from acidified potassium iodide.

* A referee has suggested that the formation of tetralone directly (*i.e.* not by a chain mechanism) is better expressed by



Then any $C_{10}H_{11}O{\cdot}O^-$ ions formed would have reacted by (11).

"AnalaR" sodium hydroxide and "AnalaR" mono- and tri-chloroacetic acid were used directly. "AnalaR" acetic acid and dichloroacetic acid were fractionally distilled once, and nitrobenzene, chlorobenzene, ethylene glycol, and "AnalaR" pyridine twice, in a stream of nitrogen.

The amount of polymerisation of acrylonitrile was determined as before (Tipper, *J.*, 1952, 2966).

The authors thank Dr. T. R. Bolam for helpful comments.

CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH.
[Present address (C. F. H. T.): DEPARTMENT OF INORGANIC AND PHYSICAL CHEMISTRY, THE UNIVERSITY, LIVERPOOL.] [*Received, August 27th*, 1953.]

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVI. Unimolecular Menschutkin Reactions in Sulphur Dioxide Solution. Remarks on the Theory of Border-line Mechanisms.*

By MARJORIE L. BIRD, E. D. HUGHES, and C. K. INGOLD.

[Reprint Order No. 4729.]

As sequel to a previous investigation on the kinetics of nucleophilic aliphatic substitution by fluoride ion in *m*-chlorobenzhydryl chloride, with sulphur dioxide as solvent, the kinetics of the reactions of pyridine and triethylamine with that alkyl halide have been investigated in the same conditions. These reactions, like the fluoride-ion reaction, are essentially unimolecular, showing strong mass-law retardations; but, unlike the fluoride-ion reaction, the amine reactions show significant quantitative deviations from the strict requirements of the unimolecular mechanism. The nature of the deviations is such as to suggest that the use of the amines as substituting agents has introduced a tendency towards the bimolecular mechanism. Yet the results cannot be understood on the basis that, while most of the individual molecular acts of substitution pursue the unimolecular mechanism, some of them concurrently follow the bimolecular. The data are, however, not inconsistent with a qualitative picture of what might be expected if, in the beginnings of a general change from a unimolecular to a bimolecular mechanism, the individual molecular acts of substitution took on characters intermediate to various degrees between the two extremes.

MOST of our previous work on unimolecular nucleophilic substitution has related to reactions in hydroxylic solvents, whose polar groups are outstanding in the strength of their attraction for ions. The conclusions reached have been summarised in a mechanistic picture of the formation and reactions of the carbonium ion in such solvents (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). The other class of solvents that might conceivably support some form of unimolecular substitution, even though such solvents are, on the whole, less solvating than are hydroxylic solvents, are the polar aprotic solvents, such as sulphur dioxide, nitromethane, and acetonitrile, that is, solvents having large dipoles in small molecules, but no exposed protons. Work on nucleophilic substitution in solvents of this class was begun with solvent sulphur dioxide during the late 1930's, was then interrupted, but has since been resumed, while parallel studies with other solvents of the class have been commenced.

The work of the 1930's relating to solvent sulphur dioxide (Bateman, Hughes, and Ingold, *J.*, 1940, 1011, 1017) is reviewed here so as to give the observational and interpretative background of the developments reported in the present three papers. First, a semi-quantitative survey was made of initial rates of substitution in benzhydryl chloride,†

* Part XXXV, *J.*, 1952, 2499.

† The long-established name, benzhydryl chloride, is convenient for discussions such as the present one, particularly when these involve also substituted derivatives. The systematic names, based on diphenylmethyl chloride and recommended by I.U.P.A.C., will be used for description of individual compounds. ED.

and in *m*-chlorobenzhydryl chloride, using a variety of substituting agents—fluoride ion, iodide ion, pyridine, triethylamine, and water. At this stage, no attempt was made to define the somewhat complex kinetic forms of the reactions, or to correct measured rates to conditions of ideality. The object was to discover whether the rates differed widely, as would be expected if the substitutions were bimolecular, or whether the rates with different substituting agents were identical to within a range of deviations conceivably due to non-ideality, as should be the case if the substitutions were all unimolecular and rate-controlled by the same ionisation. It was found that the rates with different substituting agents, although not identical, were all of the same order of magnitude, a result which told somewhat strongly against the bimolecular mechanism, whilst it allowed, without providing a quantitative test for, a unimolecular interpretation.

The next task was to elucidate the kinetic forms of some of the substitutions, not only because this itself should shed light on mechanism, but also in order that idealised rates could be computed and the test of identity of unimolecular rates applied quantitatively. The second of the previous papers reported a detailed study of the kinetics of one such reaction, *viz.*, the substitution of *m*-chlorobenzhydryl chloride by fluoride ions, supplied as tetramethylammonium fluoride, in sulphur dioxide solvent at −10·75°.

This reaction had no simple kinetic order, but showed three striking kinetic features. With raised initial concentrations of tetramethylammonium fluoride, it started more rapidly, though not nearly to the extent of a unit of kinetic order, an 18-fold concentration increase, for example, producing only a 3-fold rate increase. Then, the reactions, however rapidly they might start, were soon proceeding relatively slowly, much more slowly than could be ascribed to the consumption of reagents or the approach to equilibrium—for example, 5 times more slowly after only one-fifth of the realisable reaction. Furthermore, when tetramethylammonium chloride was initially introduced along with the corresponding fluoride, the reaction started much more slowly—for instance, by 21 times when the chloride ion was made equivalent to fluoride ion; and thereafter reaction continued with a much less pronounced progressive retardation.

These results were interpreted as illustrating unimolecular substitution, in the general case in which the ionisation step is significantly reversed, the overall-forward process containing two forward steps (1) and (3), of which step (1) is rate-controlling, together with one retrograde step (2), as follows:

$$\mathrm{AlkCl} + \mathrm{F^-} \underset{(2)}{\overset{(1)}{\rightleftharpoons}} \mathrm{Alk^+} + \mathrm{Cl^-} + \mathrm{F^-} \xrightarrow{(3)} \mathrm{AlkF} + \mathrm{Cl^-} \quad . \quad . \quad . \quad . \quad (S_N1)$$

The increase in initial rate with increasing concentration of the ionic reagent was attributed to a primary salt effect, which we could approximately calculate from our previous work on the unimolecular reactions of benzhydryl halides in aqueous solvents, by taking account of the difference of solvent with the aid of electrostatic theory. The progressive retardation of the continuing reaction, and the initial retardation produced by initially added tetramethylammonium chloride, as well as the weakened further retardation which then characterise the subsequent reaction, were consistently interpreted as effects of formed or added chloride ion in reversing the ionisation of the alkyl chloride.

The equation which gave a quantitatively satisfactory common description of the spontaneous retardations, and of the rate depressions induced by the addition of chloride ion, was the general kinetic equation of a unimolecular reaction,

$$\mathrm{d}x/\mathrm{d}t = k_1(a - x)(c - x)/\{\alpha(b + x) + (c - x)\}$$

or, in its integrated form,

$$kt(a - c) = \alpha(b + c)\ln\{c/(c - x)\} + \{(a - c) - \alpha(a + b)\}\ln\{a/(a - x)\}$$

where a, b, and c, are the initial concentrations of the alkyl halide, the displaced halide ion, and the substituting agent, respectively, and x is the concentration converted at time t. Two constants are involved, k_1 the rate-constant of step 1, which broadly determines the absolute rates, and the retardation constant α, the ratio of the rate-constant of step 2 to that of step 3, which governs the retardations, spontaneous and induced.

Before a parallel study could be undertaken of a reaction of *m*-chlorobenzhydryl chloride with an amine in sulphur dioxide, an ancillary investigation had to be made, which has already been reported (Bateman, Hughes, and Ingold, *J.*, 1944, 243), into the condition of the amine molecule in sulphur dioxide solution. For it was known that amines form complexes with the solvent, and a theory had been promulgated to the effect that two amine molecules are combined in each such complex: this, if true, would have altered fundamentally an interpretation of kinetic results. However, it was shown by analysis, combined with ebullioscopic determinations of molecular weight, and measurements of electrical conductance, that the complexes have the composition NR_3SO_2, and that they are monomeric and essentially undissociated. Thus we know that one molecule of amine is present in each kinetically separate particle containing amine, and that, even though there is a specific solvation, the kinetically significant concentration of solvated amine is identical with the stoicheiometric molecular concentration of the amine The complexes do undergo slight homolytic dissociation into their components, as could be told from the appreciable partial vapour pressures of the latter, when together present in stoicheiometric ratio, excess of solvent having been removed. In addition, the complexes undergo some electrolytic dissociation in the sulphur dioxide solvent, to give ions, the precise nature of which is still unsettled. However, this also is a minor dissociation: the two amines used in the kinetic investigation now to be described, when at the concentrations employed, show conductances of the order of only 1% of those of typical strong electrolytes at similar concentrations.

In continuation of the earlier work on substitution in *m*-chlorobenzhydryl chloride by fluoride ion in sulphur dioxide, a study has been made of the kinetics of the reactions of the same alkyl chloride with pyridine and with triethylamine in that solvent, the temperature (−10·75°) being the same as before in order that rate constants for the reactions of the three substituting agents would be directly comparable. It had first to be determined whether the substitutions by the two amines, like the reaction of fluoride ion, are of unimolecular type:

$$\mathrm{AlkCl} + \mathrm{NR_3} \underset{2}{\overset{1}{\rightleftharpoons}} \mathrm{Alk^+} + \mathrm{Cl^-} + \mathrm{NR_3} \xrightarrow{3} \mathrm{AlkNR_3^+} + \mathrm{Cl^-} \quad . \quad . \quad . \quad (S_N1)$$

step 1 being rate-controlling; or whether the reactions of these strongly nucleophilic substituting agents are one-stage bimolecular processes:

$$\mathrm{AlkCl} + \mathrm{NR_3} \longrightarrow \mathrm{AlkNR_3^+} + \mathrm{Cl^-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N2)$$

As before, the substitutions were kinetically followed by the changes in the electrical conductance of the solutions, as interpreted with the aid of empirically constructed calibration curves connecting the conductances with the concentrations of the products of substitution, in the presence of various concentrations of the materials introduced initially.

We shall explain in detail below that the reactions of pyridine and of triethylamine showed kinetic characteristics qualitatively similar to those of the reaction of fluoride ion, but with certain quantitatively distinctive effects, which we believe to signify mechanistic modifications of a more finely graded nature than would correspond to a simple switch from the unimolecular to the bimolecular mechanism of substitution.

The initial specific rates, $k_0 = (\mathrm{d}x/\mathrm{d}t)_{t=0}/a$, of any of these reactions, in the absence of initially added chloride ion ($b = 0$), should, if the substitutions are simply unimolecular, be equal to the rate constant k_1 of step 1 in that mechanism, that is, of the alkyl halide ionisation common to all the substitutions. Therefore, apart from salt effects, the initial rates k_0 of the different substitutions should be equal to one another and independent of reagent concentrations. If, however, some of the substitutions are bimolecular, then their initial specific rates k_0 should be equal to the second-order rate constant, different for each such substitution, of this one-stage mechanism, multiplied into the initial concentration of the substituting agent, in symbols, k_2c. And thus the initial specific rates, k_0, although different for the different substitutions following this mechanism, should for each of them converge on zero as the reagent concentration is diminished. If unimolecular

and bimolecular reactions run concurrently, then the rates k_0 should converge on a common finite value, as the concentration c is diminished.

Some initial specific rates of the reactions of *m*-chlorobenzhydryl chloride with pyridine and with triethylamine are given in Table 1. In Fig. 1, these values are compared with those previously recorded for the reaction with fluoride ion. It will be seen that the rates of the reaction with pyridine are about 3—5 times larger than those of the reaction with fluoride ion. The rates of the reaction with triethylamine are still larger, about 5—7 times larger than for the reaction with fluoride ion. These differences of rate, although small having regard to the general chemical differences between the reagents, are clearly real, and must be of significance for mechanism. Yet we see that, within the range of the observations, the initial specific rates of the different reactions tend neither to zero nor to any common finite value, as the reagent concentrations are diminished.

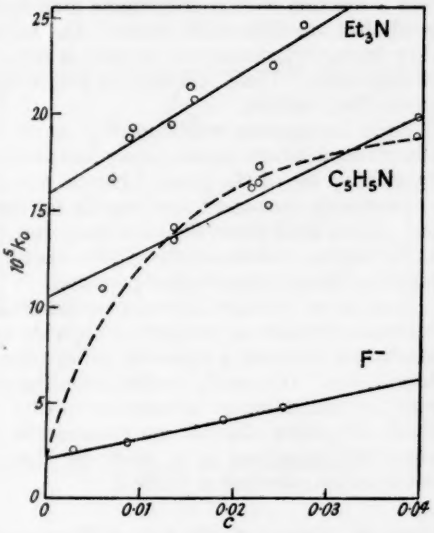


FIG. 1. *Nucleophilic substitution in* m-*chlorobenzhydryl chloride by fluoride ion, pyridine, and triethylamine, in sulphur dioxide at* −10·75°: *initial specific rates* (k_0 *in sec.*$^{-1}$) *of reaction of the alkyl chloride as functions of the concentrations* (*c in mole*/*l.*) *of the substituting agents.*

For explanation of the broken (*exponential*) *curve see p.* 640.

As shown in Fig. 1, the initial specific rates of the reactions with the amines increase with the initial concentrations of the amines, for instance, by about 2-fold for a 7-fold increase in the concentration of pyridine, and by 1·5-fold for a 4-fold increase in that of triethyl-

TABLE 1. *Initial specific rates* (k_0 *in sec.*$^{-1}$) *of reactions of* m-*chlorobenzhydryl chloride with pyridine and with triethylamine in sulphur dioxide at* −10·75°.

Pyridine				Triethylamine			
No.	[RCl]	[Amine]	10^5k_0	No.	[RCl]	[Amine]	10^5k_0
22	0·0427	0·0058	10·9	33	0·0520	0·0067	16·5
19	0·0428	0·0058	10·9	27	0·0460	0·0084	18·7
17	0·0432	0·0135	14·1	26	0·0465	0·0088	19·1
14	0·0433	0·0135	13·4	28	0·0447	0·0130	19·3
12	0·0433	0·0218	16·1	34	0·0520	0·0150	21·4
16	0·0446	0·0225	16·4	31	0·0540	0·0157	20·7
13	0·0446	0·0225	17·2	24	0·0420	0·0240	22·5
15	0·0471	0·0237	15·2	25	0·0473	0·0274	24·8
18	0·0396	0·0395	19·8				
21	0·0396	0·0396	18·8				

amine, the rate increase in either case being much smaller than would correspond to a unit of kinetic order in the substituting agent. But, because both pyridine and triethylamine are only weak electrolytes in sulphur dioxide, the rate increases are very much greater

than could be attributed to salt effects. Evidently these rate increases must be assigned to some other cause.

Even when a reaction with pyridine starts quickly, it is soon going forward quite slowly. This spontaneous progressive retardation is considerably stronger than that observed in the reaction with fluoride ions. A reaction with pyridine may typically be found, after not much more than one-tenth of its realisable course, to be continuing 10 times more slowly than it started. The kinetic effect of chloride ion, initially added as tetraethylammonium chloride, is similarly enhanced in the pyridine reaction. Thus the initial rate is reduced by about 60 times when the added chloride is equivalent to the pyridine. The continuing reaction then shows a much reduced progressive retardation, but still one which is stronger than for the fluoride-ion reaction. In the reaction of triethylamine, both the spontaneous progressive retardation, and the retardations induced by initial additions of chloride ion, are considerably smaller than in the reaction of pyridine. Thus a reaction with triethylamine may typically be going with one-quarter of its initial speed after one-fifth of its course. The initial reaction rate is reduced by about 17 times when tetraethylammonium chloride is initially introduced in quantity equivalent to the triethylamine. These retardations are, indeed, slightly milder than those applying to the fluoride-ion reaction.

As in the reaction with fluoride ions, so in these amine reactions, the spontaneous and induced retardations are obviously inexplicable on any scheme of bimolecular substitutions. By making use of the general kinetic equations for unimolecular substitution (p. 635), we previously accounted very exactly for the retardations found in the reaction of fluoride ion. As we shall show, the same procedure, when applied to the reactions of pyridine and triethylamine, leads to results which describe the general situation well, though with not quite the former quantitative precision.

Just as we obtained the main unimolecular rate constants k_1 from the initial rates of reactions in which no extraneous chloride ion had been introduced, so we may find the retardation constant α from the initial rates of reactions started in the presence of added chloride ion. It is easily verified from the equations given that, if ρ is the ratio b/c of the initial concentration of chloride ion to that of the amine, and if f is the factor $k_0^{(b)}/k_0$ by which the added chloride ion reduces the specific rate, then α is given by $(f^{-1} - 1)/\rho$. Some determinations of α, made by this method, for the pyridine and triethylamine reactions are recorded in Table 2.

TABLE 2. *Initial specific rates ($k_0^{(b)}$ in sec.$^{-1}$) of reactions of* m*-chlorobenzhydryl chloride with pyridine and with triethylamine in the presence of tetraethylammonium chloride in solvent sulphur dioxide at* $-10{\cdot}75°$.

No.	[RCl]	[Amine]	[Salt]	ρ	$10^5 k_0^{(b)}$	f	α	Mean
			Pyridine					
41	0·0385	0·00523	0·00138	0·264	0·656	0·0560	64	60
42	0·0482	0·00657	0·00178	0·271	0·608	0·0506	69	
43	0·0444	0·0223	0·00047	0·0211	7·40	0·467	54	
44	0·0570	0·0272	0·00066	0·0243	7·01	0·413	58	
46	0·0463	0·0234	0·00086	0·0367	5·18	0·324	57	
			Triethylamine					
36	0·0526	0·0056	0·00234	0·418	2·47	0·140	14·7	16
37	0·0507	0·0056	0·00111	0·198	3·55	0·202	19·8	
39	0·0510	0·0150	0·00040	0·0267	14·7	0·720	14·7	
40	0·0426	0·0125	0·00041	0·0328	13·7	0·695	13·4	

In these determinations of the constants k_1 and α, we have in principle made no use, and in practice only a slight use, of the kinetic forms of the reactions; and thus it is allowable to employ the constants in order to calculate kinetic forms. It is also permissible to compare the results of such calculations with experimentally observed kinetic forms from the beginnings of reaction up to points earlier than those at which the overall retrograde reaction, which we have not yet studied separately, could disturb the measured rate. In the reactions of the two amines with *m*-chlorobenzhydryl chloride, the equilibria lie

well over on the side of the *m*-chlorobenzhydryl-pyridinium and -triethylammonium ions; * and consistently, our study of the kinetics indicates that at least the first 10—20% of these reactions, as conducted, can be treated as free from disturbances by the retrograde substitutions.

For the reactions of pyridine and triethylamine, it was found that, whilst the equation of the unimolecular mechanism reproduces the observed course of reaction incomparably better than does that of the bimolecular mechanism, both equations being fitted to the same initial rate, the unimolecular equation does not quite repeat the perfection of its performance on the fluoride-ion reaction. The general concordance, and detailed deviations, are illustrated in Fig. 2. However, we think that these quantitative discrepancies do not affect our main conclusion that the approximate agreement of the observations with the unimolecular equation demonstates the essentially unimolecular nature of the amine substitutions. The disturbances might be connected with the finer modifications of mechanism that we shall discuss below, but they might represent neglected effects of non-ideality, or some experimental systematic error.

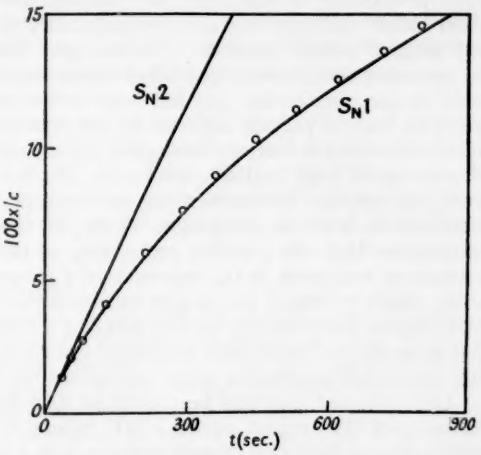


FIG. 2. *Kinetic course of reaction of* m-*chlorobenzhydryl chloride with triethylamine in sulphur dioxide at* −10·75° (*part of run* 35).

The summary of our findings is that the substitutions by amines show the most diagnostic kinetic feature of the unimolecular mechanism, the common-ion retardations, but deviate from the requirements of that mechanism in at least two important respects. First, the rates are sensitive to the nature of the substituting agent, though not nearly as sensitive as would be expected of bimolecular reactions. Secondly, the rates are affected by the concentrations of the reagents, though not nearly to the extent appropriate to bimolecular reactions.

It seems clear that, in moving over, with strongly nucleophilic substituting agents, from hydroxylic solvents to a polar aprotic solvent, we have not changed a unimolecular into a bimolecular substitution, but that we have introduced into the unimolecular reactions some variation of mechanism suggestive of a partial incursion of bimolecular character. If, however, we try to specialise this conclusion by assuming that, whilst most of the individual molecular acts of substitution pursue the unimolecular mechanism, some of them concurrently follow the bimolecular mechanism, an obvious difficulty arises. For then it

* We did not make any actual determinations of the position of equilibrium, but we did follow a number of the runs to more than 70% of their stoicheiometrically possible course, when they were still going forward slowly. The difficulty in determining equilibrium compositions by the technique used for the kinetic measurements arose from the circumstance that, for convenience in filling, our conductivity cells were only stoppered, and not hermetically sealed, with the result that a slow escape of the sulphur dioxide solvent began, after some time, appreciably to alter concentrations, thereby limiting significant conductance measurements to periods of about one day. These reactions, even though they may start rapidly, go so slowly in the later part of their course that many days would have been needed in order to establish a close approximation to equilibrium.

cannot be understood why rates which are sensitive to the nature of the substituting agent when the concentration of the latter is high, are, as Fig. 1 shows, hardly less sensitive when the concentration is low. This hypothesis of concurrent S_N1 and S_N2 processes would require Fig. 1 to exhibit three straight lines diverging from a common point on the rate axis.

We prefer to assume that, as was foreseen long ago (Hughes, Ingold, and Patel, *J.*, 1933, 526; Gleave, Hughes, and Ingold, *J.*, 1935, 236), the beginnings of a change from a unimolecular to a bimolecular mechanism are such that the individual molecular acts of substitution take on individual characters intermediate to various degrees between the two extremes of mechanism. We can then understand, though as yet only in a qualitative way, the general pattern of Fig. 1, in particular the seeming paradox that the sensitivity of rate to the nature of the reagent is itself insensitive to the reagent concentration.

Consider the following crude but simple model. We will assume that, in bimolecular substitution, an alkyl halide molecule has a negligible probability of decomposition, unless a reagent particle is localised to within a very small volume beside it, and that then it has a large probability of reaction. We assume also that, in unimolecular substitution, the alkyl halide molecule has a large probability of decomposition, independently of where any reagent particle may be. We can give these two situations a common description by assuming that, around any alkyl halide molecule, a certain volume v, which would be small in the bimolecular case but large in the unimolecular, can be described, such that, when no reagent particle is inside it, the probability of decomposition of the alkyl halide molecule is small at best, whereas when at least one reagent particle is within, the probability of reaction is large and characteristic. By now allowing v to vary without restriction from one reaction to another, we can conceptually connect the two limiting molecular mechanisms with a continuous chain of intermediate mechanisms. Certainly, our assumption that the reaction probability of the alkyl halide undergoes the whole of its increase at one point in the approach of a reagent particle, is a highly artificial simplification, which we would like to give up, assuming instead probabilities which vary smoothly with reagent position, and thereby bringing a further element of continuity into our picture. But as we do not know what functional connexion to assume, this path cannot be pursued, and we are left to consider what conclusions the simpler model has to offer.

Let n reagent particles be contained in a solution of volume V, so that the concentration c of the reagent equals $n/\boldsymbol{N}V$, where $\boldsymbol{N}$ is Avogadro's number. Then the probability that at least one reagent particle is in a particular localised volume v is evidently *

$$1 - (1 - v/V)^n = 1 - e^{-c\boldsymbol{N}v}$$

provided that $v \ll V$. If k and K are respectively those specific rates of reaction of the alkyl halide, which would obtain if all alkyl halide molecules at all times had the low and the high reaction probability associated respectively with the non-occupation and the occupation of v by the reagent, then the initial specific rate corresponding to the calculated degree of occupation will be

$$(\mathrm{d}x/\mathrm{d}t)/a = k + K(1 - e^{-\beta c})$$

where $\beta = \boldsymbol{N}v$ is a constant of the reaction.

When β is small, the second term becomes $K\beta c$, and represents a reaction of first order in the reagent, and thus of second order overall. When β is large, the term becomes K, and represents a reaction of zero order in the reagent, and first order overall. Between these extremes the specific rate should rise with increasing reagent concentration, at first steeply and then ever more gently in an exponential way. Actually, we can put two exponential curves, both rising from the fluoride-ion intercept in Fig. 1, through the pyridine and the triethylamine points, without exposing deviations markedly larger than those from the best straight lines. One such curve is inserted in Fig. 1, but its introduction does not imply that our model is considered good enough to be tested by a precise mathematical form, or that our experimental data are accurate enough for such a comparison. Our main point is that the data present a picture which seems qualitatively

* The first expression followed by counting complex ions, and the second derives from the theorem that $(1 - y/r)^r$ tends to e^{-y} as r tends to infinity.

more consistent with the theory of intermediate molecular mechanisms than with that of concurrent extremes.

Winstein, Grunwald, and Jones have previously attacked the problem of distinguishing between intermediate mechanisms and concurrent extremes, and have concluded that the aqueous-alcoholysis of *iso*propyl bromide is not satisfactorily regarded as a simple concurrence of extremes (*J. Amer. Chem. Soc.*, 1951, **73**, 2700). Our own preconceptions strongly favour this conclusion, but we must add that, in our view, the authors ensured it by their procedure. Their method was to demonstrate a disagreement between the observed effect of changes of solvent on the rate of this solvolysis, and the mixture-law sum of the two computed effects, one patterned, with the aid of a linear free-energy relation, on that of bimolecular solvolysis, as of methyl or (somewhat less safely) ethyl bromide, the relevant solvent property being nucleophilic power, and the other modelled similarly on that of unimolecular solvolysis, as of *tert.*-butyl bromide, the important solvent property here being ionising power. But in re-mapping the ethyl bromide pattern of kinetic solvent effects in order to obtain the bimolecular part of those of *iso*propyl bromide, a form of free-energy relation was adopted which involved cross-correlation with the unimolecular case of *tert.*-butyl bromide (and, in fact, the adopted relation, which had to be used as if linear, was manifestly non-linear for methyl and ethyl bromide). Thus the computed component effects, whose independence and complementality were to be tested, got mixed together before the test of additivity was applied.

Our retardation constants α give the following order for the rates of attack of reagents on the *m*-chlorobenzhydryl carbonium ion, $Cl^- > NEt_3 > F^- > C_5H_5N$, the rate-ratios being as the reciprocals of the numbers 1, 16, 20, 60. From this it would seem that, for attack upon a pre-formed cation, the long-range forces of the net charge are an important determinant of the affinity of the reagent, as well as the short-range forces of its unshared electrons, and, conceivably, of steric effects.

Experimental

The preparation and purification of materials, together with the apparatus and the method of measurement, were those described by Bateman, Hughes, and Ingold (*loc. cit.*). Pyridine was purified through its zinc chloride complex. In the kinetic runs with the two amines, the amine was added to the solvent in the conductivity cell, and the electrical conductance was allowed to settle down, before the *m*-chlorobenzhydryl chloride was added and a series of readings started. Initial disturbances were minimised by care in the exclusion of moisture, as controlled by the initial freedom of the solution from the yellow colour which immediately develops when moisture does intrude.

Calibration.—Owing to the difficulty in handling dry samples of *m*-chlorobenzhydryl-pyridinium and -triethylammonium chloride, which are extremely hygroscopic, the effect of different concentrations of them on the electrical conductance was determined by causing them to be formed in various amounts in sulphur dioxide solution from suitable quantities of the reactants. After time had been allowed for the production of a salt, but always at a moment when the reaction was not going too quickly, the increment of conductance was noted, and the cell-contents were immediately cooled to $-80°$. The cooled solution was extracted with ether and water, and the aqueous chloride ion was determined by electrometric titration with silver nitrate. In this way, concentration–conductance curves were built up, first for *m*-chlorobenzhydryl-pyridinium and -triethylammonium chloride in the absence of any added salt, and then for each of them in the presence of various amounts of initially added tetraethylammonium chloride. The curves were not quite linear, and gave factors, connecting concentration increments with conductance increments, which ranged from 0·040 mole ohm cm.$^{-2}$ for *m*-chlorobenzhydrylpyridinium chloride, and 0·066 mole ohm cm.$^{-2}$ for *m*-chlorobenzhydryltriethylammonium chloride, both at low concentrations, to about double these values at the highest total salt concentrations used.

Results.—The initial specific rates are given in Tables 1 and 2. For most runs without initially added tetraethylammonium chloride, direct reading of the conductance–time graphs was found to be unreliable, owing to the large rate changes near the commencement of reaction. It was more satisfactory to read from these graphs a series of rates over the first few units per cent. of reaction, and then to plot the reciprocals of these rates against the extent of reaction, the initial rate being obtained from the axial intercept of the new graph. Independent repeti-

tions by this method gave reasonable consistency, and mean values were taken. For most runs in which tetraethylammonium chloride had been added initially, the direct and the indirect method were about equally satisfactory and we usually made several independent estimates by both methods and took a selected mean.

TABLE 3. *Kinetic course of the reaction of* m-*chlorobenzyhydryl chloride with pyridine in sulphur dioxide at* −10·75° (*run* 13).

Initially, $a = [RCl] = 0{\cdot}0446$M, and $c = [C_5H_5N] = 0{\cdot}0225$M. The product concentration is x (M) at time t (sec.). The bimolecular rate constant, k_2 in sec.$^{-1}$ mole^{-1} l., is calculated as $\{1/t(a-c)\}\ln\{c(a-x)/a(c-x)\}$. The unimolecular rate constant, k_1 in sec.$^{-1}$, is computed from the equation on p. 635 with $\alpha = 60$.

t	10^4x	$10^2x/c$	10^4k_2	10^5k_1	t	10^4x	$10^2x/c$
45	2·00	0·89	46	15·8	1,530	18·24	8·12
66	2·80	1·25	42	18·2	1,692	18·64	8·27
120	4·00	1·78	34	17·0	1,872	19·48	8·64
186	4·64	2·06	25	14·2	2,100	20·64	9·16
240	5·85	2·60	25	15·7	2,292	21·20	9·41
285	6·72	2·99	23	16·8	2,460	21·84	9·71
360	7·80	3·46	22	17·0	2,670	22·66	10·09
468	9·08	4·03	20	16·8	2,880	23·28	10·33
594	10·68	4·74	19	17·4	3,120	24·12	10·70
678	11·68	5·19	18	18·0	3,300	24·76	10·99
732	12·24	5·45	17	18·1	3,480	25·40	11·29
900	13·56	6·02	16	17·8	3,630	25·92	11·50
1080	14·84	6·80	14	17·6	3,780	26·40	11·72
1218	15·84	7·05	14	17·7	4,020	27·20	12·51
1290	16·28	7·23	13	17·5	70,200	77·76	34·50

Part of the course of a run with triethylamine is shown in Fig. 2. In further illustration of the kinetic form of these reactions, Table 3 records the followed part of a pyridine run. The calculated rate constants in the Table apply to a period well before the effects of overall reversibility begin to be apparent in the measurements.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1. [*Received, October* 15*th*, 1953.]

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVII. Halide-ion Exchange with a Simple Alkyl Halide in Sulphur Dioxide Solution.*

By C. A. BUNTON, C. H. GREENSTREET, E. D. HUGHES, and C. K. INGOLD

[Reprint Order No. 4730.]

Of the halides, methyl iodide, ethyl bromide, *iso*propyl bromide, and *tert.*-butyl bromide, only the last exchanged its halogen with tetramethylammonium fluoride in sulphur dioxide sufficiently rapidly for observation in the conditions used, and this reaction had the kinetic characteristics of a unimolecular substitution. Its specific rate depended on the concentration of the reagent only to such an extent as could be quantitatively understood as the expected salt effect in a unimolecular substitution with an ionic substituting agent. The common-ion retardation of the unimolecular mechanism, was considerably smaller than in non-solvolytic benzhydryl substitutions, but was quite large enough to be measured, in contrast to solvolysis in which such retardation, although large enough for measurement in the benzhydryl series, is too small for observation with *tert.*-butyl bromide.

OUR early investigation (cf. preceding paper) of substitution of benzhydryl halides in solvent sulphur dioxide was unsystematic in that we had not previously examined reactions of the simplest alkyl halides, an omission to some extent repaired by the work recorded in this and the following paper. Here we deal with the reaction of halide-ion exchange, using as before electrical conductance as a method of following the progress of reaction.

* Part XXXVI, preceding paper.

First, a qualitative survey was made of the behaviour of fluoride ion, supplied as tetramethylammonium fluoride in sulphur dioxide, towards methyl iodide, ethyl bromide, *iso*propyl bromide, and *tert.*-butyl bromide in the temperature range −20° to +15°, the lower limit being determined by the performance of our thermostat, and the upper by the safety of our conductivity cells under the vapour pressure developed by the solvent. It was found that the reaction between fluoride ion and the methyl, ethyl, or *iso*propyl halide was too slow to be measured in these conditions, but that a reaction occurred with *tert.*-butyl bromide, which was conveniently measurable near the lower end of the temperature range, but somewhat fast near the upper end.

These facts alone have significance for the mechanism of the reaction of fluoride ion with the *tert.*-butyl halide. In the next paper we shall report a bimolecular reaction between pyridine and methyl iodide, which is measurable at similar temperatures, and we can feel sure that a bimolecular reaction between fluoride ion and methyl iodide would be much slower, and hence too slow for measurement at such temperatures. The bimolecular reactions of fluoride ion with ethyl, *iso*propyl, and *tert.*-butyl bromide are likely, if the usual rules are followed, to be slower still in successive degrees, and so they also will be too slow to be measured. If a unimolecular reaction of any of the same four halides is fast enough to be measured, the reaction of *tert.*-butyl bromide will surely be that one. The unimolecular reactions of the *iso*propyl, ethyl, and methyl halides will be very much slower in successive degrees, and therefore they will all be too slow to be measured in similar conditions. One sees that it is hardly possible to rationalise the few qualitative observations mentioned, unless we may assume that the reaction of fluoride ion with *tert.*-butyl bromide is unimolecular.

This conclusion is supported by the study we have made of the kinetics of this *tert.*-butyl halide-ion exchange at −15·03°. Generally, the reaction exhibits kinetic features qualitatively similar to, though quantitatively different from, those shown by the reaction between fluoride ion and *m*-chlorobenzhydryl chloride (Bateman, Hughes, and Ingold, *J.*, 1940, 1017).

The first notable point is that, although the initial specific rate of conversion of *tert.*-butyl bromide rises with increasing initial concentration of fluoride ion, this effect is altogether smaller than would correspond to a unit of kinetic order in the substituting agent. For example, a doubled concentration of the tetramethylammonium fluoride added less than 10% to the rate, and a nearly 7-fold increase in the concentration of the substituting agent did not quite double the rate. The figures are in Table 1.

TABLE 1. *Initial specific rates* (k_0 *in sec.*$^{-1}$) *of reaction of* tert.*-butyl bromide with tetramethylammonium fluoride in solvent sulphur dioxide at* −15·03°.

No.	RBr	NMe_4F	10^5k_0	No.	RBr	NMe_4F	10^5k_0
62	0·0281	0·0112	5·92	69	0·0830	0·0486	9·26
65	0·0278	0·0155	6·37	66	0·0253	0·0543	9·52
61	0·0280	0·0214	6·49	68	0·0805	0·0602	10·60
51	0·0304	0·0215	6·36	58	0·0305	0·0702	10·68
63	0·0255	0·0266	6·83	59	0·0280	0·0742	11·50
64	0·0257	0·0397	7·52				

This slow rise in the specific rate of conversion of the alkyl halide with increasing concentration of the reagent can very plausibly be ascribed to the positive salt effect expected in unimolecular substitution with an ionic reagent. The effect has a functional form which agrees with this interpretation, and a magnitude close to what could be calculated, with the aid of electrostatic theory, from known salt effects in the solvolytic unimolecular reactions of *tert.*-butyl bromide. The theory of the matter has been already given (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979), and need not be summarised, except with respect to the conclusions, which are as follows. The proportional rate change for a given change in the ionic strength μ depends on the solvent essentially through its macroscopic dielectric constant D, and otherwise on the conditions of reaction exclusively through the absolute temperature T. It depends on the substance undergoing the unimolecular reaction only through a molecular constant of the dimensions of length, which measures in

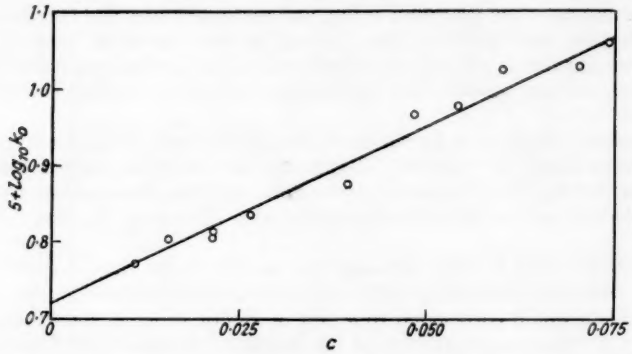
a special way the amount of electron displacement in the transition state of the rate-controlling ionisation. This quantity σ is essentially a constant of the ionising molecule, and, as an approximation, may be carried over unchanged from one solvent to another; but, in closer approximation, it is expected also to be somewhat dependent on the solvent, because the weaker the solvation of the partly formed ions of the transition state, the larger the internal transfer of electrons has to be in order to determine the breakage of the bond. A quantitative expression of the electrostatic theory is contained in the equation,

$$k_1^{\mu} = k_1^{0} \text{ antilog}_{10} (0{\cdot}912 \times 10^{16}\mu\sigma/D^2T^2)$$

where k_1^{μ} is the unimolecular rate constant at ionic strength μ, and k_1^{0} is the limit to which it goes at zero ionic strength. This shows that the plot of $\log_{10}k_1^{\mu}$ against μ should be a straight line, its axial intercept being $\log_{10}k_1^{0}$, and its slope $0{\cdot}912 \times 10^{16}\sigma/D^2T^2$.

We can identify k_1^{μ} with the values of $k_0 = (dx/dt)_{t=0}/a$ in Table 1, and the relevant ionic strength μ as the introduced concentration c of tetramethylammonium fluoride. Calling k_0^{0} the limit into which k_0 goes when c tends to zero, substituting $D = 16{\cdot}7$ and

Logarithm of the initial specific rate of reaction of tert.*-butyl bromide with tetramethylammonium fluoride in sulphur dioxide at −15·03°, plotted against the initial salt concentration.*



$T = 258°$, and expressing σ for convenience in Ångstrom units, our theoretical equation takes the form,

$$\log_{10}k_0 = \log_{10}k_0^{0} + 4{\cdot}92\sigma c$$

For aqueous reactions the constant σ of *tert.*-butyl bromide has been found to be about 0·80 Å. For reactions in sulphur dioxide we might, for the reason given above, expect a slightly larger value.

The plot of $\log_{10}k_0$ against c is shown in the Figure. It is linear to within the experimental error. The slope of the line gives the reasonable σ value, 0·93 Å. The axial intercept gives the rate constant k_0^{0} at infinite dilution as $5{\cdot}2 \times 10^{-5}$ sec.$^{-1}$.

On the evidence so far given, the conclusion would be justified that a unimolecular substitution is under observation; but that conclusion can be confirmed. For, in principle, such a reaction, independently of its possible overall reversibility, admits of retardation of its overall forward process, through retrogression of the rate-determining step of the latter, as influenced by the anions formed in the reaction, or by added anions of the same kind:

$$Bu^tBr + F^- \underset{(2)}{\overset{(1)}{\rightleftharpoons}} Bu^{t+} + Br^- + F^- \xrightarrow{(3)} Bu^tF + Br^- \quad . \quad . \quad (S_N1)$$

In this reaction bromide ions are formed: when bromide ions are added as tetramethylammonium bromide, the reaction rate is reduced below that appropriate to the ionic strength; and this is true from the commencement of reaction, when there can be no disturbance from the overall retrograde substitution. Obviously this is the expected mass-law retardation of the forward process by added anions of the same kind as those

formed. As noted in the preceding paper, we can calculate the retardation constant α, that is, the ratio of the specific rate of step (2) to that of step (3) of the unimolecular substitution as written above, from the factor f by which the initial specific rate is reduced, when bromide ion is added initially in a concentration ρ times that of the fluoride ion: the formula is $\alpha = (f^{-1} - 1)/\rho$. Data relating to some experiments, which allow α to be thus calculated, are given in Table 2. The retardations f are not as large as we have observed in some other unimolecular reactions, and this is expressed in the comparatively small value of α.

TABLE 2 *Initial specific rates* ($k_0^{(b)}$ *in sec.*$^{-1}$) *of the reaction of* tert.*-butyl bromide with tetramethylammonium fluoride in the presence of initially added tetramethylammonium bromide in solvent sulphur dioxide at* $-15{\cdot}03°$.

No.	[RBr]	[NMe_4F]	[NMe_4Br]	ρ	$10^5 k_0^{(b)}$	f	α
71	0·0304	0·0124	0·0139	1·12	4·84	0·717	0·35
72	0·0286	0·0209	0·0118	0·565	6·28	0·859	0·29
74	0·0291	0·0169	0·0305	1·81	5·66	0·651	0·30
76	0·0297	0·0083	0·0119	1·43	4·60	0·719	0·27
						Mean	0·30

In unimolecular hydrolysis in aqueous solvents, common-ion retardations are generally small, doubtless because here the ion, in low concentration, is in competition with water, present in quantity as a part of the solvent, in the common attack upon the carbonium ion. In the earlier study of aqueous reactions, it was indeed found that common-ion retardation in the hydrolysis of *tert.*-butyl bromide was too small to be observed, although common-ion retardations were readily observable in the hydrolysis of various simple and substituted benzhydryl halides (Bateman, Church, Hughes, Ingold, and Taher, *loc cit.*). In non-solvolytic substitutions in sulphur dioxide, the retardations are generally much larger; and this can be understood, because now the common ion is under competition only from a substituting agent in a comparably low concentration. However, within this raised scale of retarding effects, the difference between *tert.*-butyl bromide and the benzhydryl halides appears again, when we compare the present retardation constant of 0·30 for substitution by fluoride ion in *tert.*-butyl bromide, with the previously recorded constant of 20 for substitution by fluoride ion in *m*-chlorobenzhydryl chloride (Bateman, Hughes, and Ingold, *loc cit.*). The slower combination of bromide ion than of fluoride ion with the *tert.*-butyl cation, despite the faster combination of chloride ion than of fluoride ion with a benzhydryl cation, may be disclosing a steric effect in the union of large anions with tertiary carbonium ions.

The general kinetic course of the reactions of fluoride ion with *tert.*-butyl bromide in sulphur dioxide has been studied, and the details of an illustrative run are given in the Experimental section. However, owing to the smallness of the common-ion retardation, and the strong reversibility of the overall substitution, the kinetic form does not in this case provide a particularly distinctive test of mechanism. These substitutions, as we conducted them, came to approximate equilibrium in the broad neighbourhood of 50% conversion; but we could neither measure these equilibria accurately nor make a separate kinetic study of the retrograde substitution, for the reason that *tert.*-butyl fluoride decomposes in sulphur dioxide—somewhat slowly, but fast enough to spoil such measurements. Thus only the early part, certainly not more than 10%, of the forward substitution was suitable for a kinetic analysis which necessarily neglected disturbance by the retrograde reaction; and, within this limited range of progress of reaction, neither the kinetic order, nor the common-ion retardation, makes any striking difference to the reaction–time curve.

EXPERIMENTAL

On account of the hygroscopic nature of tetramethylammonium fluoride it was put into the conductivity cell first by transference, in a current of dry nitrogen, from a weighing-tube taken directly from the Abderhalden drier into the cell taken directly from its drying oven. Tetramethylammonium bromide, when used, was handled similarly. Dry sulphur dioxide was passed through the cell as gas for some time, before the temperature was reduced, and it was

collected as liquid. The purified *tert.*-butyl bromide, taken from a freshly opened ampoule, was added finally from a weight-pipette.

Calibration.—It was shown by experiments with synthetic mixtures of tetramethylammonium fluoride and bromide, that the replacement of a proportion of one of these salts by its equivalent of the other produced, for any fixed total salt concentration, a conductance change proportional to the amount so replaced, although the proportionality constant varied with the total salt concentration. Hence, for calibration, it was sufficient to determine the conductances of the two salts separately, over the relevant concentration range. These data are in Table 3.

TABLE 3. *Electrical conductance (κ in ohm^{-1} cm.$^{-1}$) of tetramethylammonium fluoride and of tetramethylammonium bromide in sulphur dioxide at* −15·03°

NMe_4F				NMe_4Br			
Concn. (M)	$10^3\kappa$	Concn. (M)	$10^3\kappa$	Concn. (M)	$10^3\kappa$	Concn. (M)	$10^3\kappa$
0·00311	0·336	0·0540	2·77	0·00330	0·428	0·0235	2·16
0·00341	0·356	0·0573	2·97	0·0071	0·774	0·0333	2·87
0·0244	1·47	0·0752	3·87	0·0090	0·948	0·0522	4·22
0·0252	1·55	0·109	5·83	0·0146	1·42	0·0579	4·76
0·0340	1·96	0·115	6·05	0·0152	1·46	0·0868	6·48

From these figures curves were drawn, one for the electrical conductance of each salt *versus* its concentration. Then a curve was drawn for the difference in the conductances of the two salts at different common concentrations. The ratios of the ordinates to the abscissæ of this third curve, when plotted against the abscissæ, gave the rate of change of conductance with the concentration in which one salt was replaced by its equivalent of the other $d\kappa/dx$, as a function of the total salt concentration μ. Actually it was more convenient to make this fourth plot one of the reciprocal of the above derivative, namely, $dx/d\kappa$, against μ, since the ordinates were then the factors by which each measured conductance change, at a known total salt concentration, had to be multiplied in order to give the corresponding concentration of material converted.

Results.—As usual, both methods of getting initial specific rates, *viz.*, direct reading, with a reflecting straight edge, from the conductance–time curves, and extrapolation from calculated, slowly drifting "constants," were tried; but in these experiments the direct method was preferred, as the initial curvatures were not excessive, whereas random scatter among the first few calculated constants often left a doubt about how the extrapolation should be made. The results of the measurements are in Tables 1 and 2.

An illustration is given in Table 4 of the kinetic form of a run. It will be noted that the unimolecular rate constants k_1, calculated with due allowance for the common-ion effect, by the equation given in the preceding paper, show fair constancy over the first 8% of reaction, but after that fall. This fall is due essentially to the overall reversibility of the substitution

TABLE 4. *Illustrating the kinetic course of the reaction between* tert.*-butyl bromide and tetramethylammonium fluoride in sulphur dioxide at* −15·03°. (*Run* 68.)

{Initially, a = [RBr] = 0·0805M, and c = [NMe_4F] = 0·0602M. The product concentration is x (M) at time t (sec.). The unimolecular rate constants (k_1 in sec.$^{-1}$) are calculated with α = 0·30 from the equation in the preceding paper (p. 635).}

t	10^3x	$10^3x/c$	10^5k_1	t	10^3x	$10^3x/c$	10^5k_1
120	1·15	1·91	11·1	1260	9·38	15·6	10·1
240	2·05	3·41	10·7	1800	12·37	20·6	9·6
360	2·92	4·85	10·6	3600	19·6	32·6	8·3
480	3·96	6·58	10·5	4800	22·6	37·6	7·5
600	4·81	8·00	10·5	6000	25·6	42·5	7·0

10^5k_1 from mean of first five readings = 10·6
10^5k_0 from reaction–time graph = 10·6

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1.

[*Received, October 15th*, 1953.]

Mechanism of Substitution at a Saturated Carbon Atom. Part XXXVIII. Menschutkin Reactions of Some Simple Alkyl Halides in Sulphur Dioxide Solution.*

By C. A. Bunton, C. H. Greenstreet, E. D. Hughes, and C. K. Ingold.

[Reprint Order No. 4731.]

The reaction between methyl iodide and pyridine in sulphur dioxide to form methylpyridinium iodide is of second order, and is evidently a bimolecular nucleophilic substitution. Similar reactions of ethyl iodide and of *iso*propyl bromide with pyridine were too slow for kinetic observation. That of *tert.*-butyl bromide with pyridine to form *iso*butylene and pyridinium bromide has the kinetic characteristics of a unimolecular reaction; in particular, it shows a strong common-ion retardation. However, the rate depends slightly on the reagent concentration; and comparison with the similarly unimolecular reaction of *tert.*-butyl bromide with fluoride ion shows that the rate depends appreciably on the nature of the reagent, and that this dependence is but little influenced by the concentration of the latter. These relations are similar to those observed in the unimolecular substitutions of *m*-chlorobenzhydryl chloride in sulphur dioxide, and are thought to indicate that, when the solvent has not the large margin of ionising power required to support unimolecular mechanisms in their limiting and simplest forms, then at least some of the individual molecular acts of conversion follow paths in which the reagent assists the ionising solvent to varying degrees.

We report here a study of some reactions of simple alkyl halides with pyridine in solvent sulphur dioxide. As in other kinetic studies with that solvent, we have followed the progress of reaction by the associated changes in electrical conductance.

Our first step was to make a qualitative survey of the behaviour of methyl iodide, ethyl iodide, *iso*propyl bromide, and *tert.*-butyl bromide, towards pyridine in sulphur dioxide within the temperature interval, $-20°$ to $+15°$, to which (see preceding paper) we were limited by our apparatus. Methyl iodide underwent a reaction which was somewhat slow, but nevertheless fast enough to permit determination of initial rates. The reactions of ethyl iodide and of *iso*propyl bromide were too slow to be observed: they must have been slower than the reaction of methyl iodide by at least one order of magnitude. *tert.*-Butyl bromide, on the other hand, underwent a reaction which was somewhat rapid, though its rate could be measured near the lower end of the available temperature range.

In the light of our general knowledge of nucleophilic substitution and elimination, these observations strongly suggest that the reaction of methyl iodide with pyridine is bimolecular, whilst that of *tert.*-butyl bromide with pyridine is unimolecular. For on ascending the homologous series of alkyl groups, we expect bimolecular rates to fall; and therefore, after methyl, for which the rate is already small, it is very likely to become too small for measurement. Concurrently, the unimolecular rates are expected to rise by large ratios along the series; but it is apparent that only with the last member, *tert.*-butyl bromide, does the rate ascend into the observable range of magnitudes.

Kinetic examination of the reactions of methyl iodide and of *tert.*-butyl bromide with pyridine in sulphur dioxide confirmed this preliminary diagnosis. It also disclosed that the reaction of *tert.*-butyl bromide, whilst it has in well-developed form the main kinetic characteristics of the unimolecular mechanism, shows quantitative peculiarities, which are generally similar to those, described in Part XXXVI (*J.*, 1954, 634), of the reaction of *m*-chlorobenzhydryl chloride with amines, and are thought to represent an appreciable limitation to the preference of the solvent for creating ions without accepting help from strongly nucleophilic solutes.

The present kinetic work has been done at $-15{\cdot}03°$, the temperature of the experiments, described in the preceding paper, on the reaction of *tert.*-butyl bromide with fluoride ion.

* Part XXXVII, preceding paper.

It was found a convenient enough temperature for initial rate measurements on the reaction of methyl iodide with pyridine; and, by using it for the reaction of *tert.*-butyl bromide with pyridine, we could compare the rates of reaction of this alkyl halide with the two reagents. This comparison is of significance in the discussion of the mechanisms of these processes.

Kinetics of the Reaction of Methyl Iodide with Pyridine.—As explained in Part XXXVI, the circumstance that our conductivity cells could not easily be made gas-tight limited the duration of kinetic runs to periods of about a working day. In that time, the proportional progress of the reaction between methyl iodide and pyridine was only of the order of 1%. Thus we were restricted to the measurement of initial rates. Our observed conductance–time curves were straight lines, whose slopes gave initial rates, and, when divided by the initial concentration of the methyl iodide, measured specific rates, as recorded in Table 1.

TABLE I. *Initial rates of reaction of methyl iodide with pyridine in sulphur dioxide at* −15·03° *as measured by the change in the electrical conductance.*

(The specific conductance κ is in ohm^{-1} cm.$^{-1}$, the concentrations a and c are in mole/l., and the time t is in sec.)

No.	a, [MeI]	c, [C_5H_5N]	$10^4\frac{d\kappa}{dt}$	$10^3\frac{d\kappa}{dt}/a$	No.	a, [MeI]	c, [C_5H_5N]	$10^4\frac{d\kappa}{dt}$	$10^3\frac{d\kappa}{dt}/a$
87	0·0376	0·0734	0·183	0·49	85	0·0619	0·1029	0·422	0·68
88	0·0863	0·0870	0·552	0·64	91	0·0811	0·2187	1·23	1·51
89	0·0751	0·1017	0·472	0·63	90	0·0809	0·4581	2·37	2·93

These initial specific rates of increase of conductance are really first-order rate constants in non-standard units, differing from the conventional constants only by a uniform factor of calibration, which we did not determine for this reaction, because we had no other reaction of the same kinetic form with which we wanted to compare it with respect to rate. Plotting the initial specific rates against the concentration of pyridine gave a straight line which passed through the origin (see Fig. 1). This presents a striking contrast to the two given below for reactions of *tert.*-butyl bromide, and to three given in Part XXXVI for substitutions of *m*-chlorobenzhydryl chloride. It demonstrates that the reaction of methyl iodide with pyridine in sulphur dioxide is a second-order process.

We conclude that this reaction, the product of which was shown to be methylpyridinium iodide, is a bimolecular nucleophilic substitution in solvent sulphur dioxide:

$$MeI + C_5H_5N \longrightarrow MeNC_5H_5^+ + I^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N2)$$

Kinetics of the Reaction of tert.*-Butyl Bromide with Pyridine.*—Although the rates of the reactions of pyridine and of fluoride ion with methyl iodide are of different orders of magnitude, that of the latter being unobservably small, the rates of the reactions of these two reagents with *tert.*-butyl bromide are similar; but they are not identical. If we compare the initial specific rates of reaction of *tert.*-butyl bromide with pyridine (see Table 2) with the corresponding quantities for the reaction of this bromide with fluoride ion (see Table 1 of the preceding paper, p. 634), we see that the pyridine rates are 2—3 times the fluoride-ion rates. Here, the solvent and temperature are the same; and although there is a difference of ionic strength, this cannot be held responsible for the rate difference, since its direction is such as would reduce the observed difference.

TABLE 2. *Some initial specific rates* (k_0 *in sec.*$^{-1}$) *of reaction of* tert.*-butyl bromide with pyridine in sulphur dioxide at* −15·03°.

No.	[Bu^{t}Br]	[C_5H_5N]	10^5k_0	No.	[Bu^{t}Br]	[C_5H_5N]	10^5k_0
102	0·0336	0·0091	17·5	108	0·0429	0·0420	24·0
103	0·0396	0·0173	20·0	106	0·0334	0·0432	21·5
97	0·0526	0·0414	22·0	107	0·0360	0·0438	23·5

In the graphical comparison in Fig. 2, we observe, first, that the rate of the pyridine reaction appears to increase with the pyridine concentration. The increase is too much to be understood as an ionic-strength effect, since initial ionic strengths in this reaction are quite low. But it is much too small to represent a unit of kinetic order with respect to pyridine. We see also that, whilst the rates of the pyridine and fluoride-ion reactions

are different, the difference does not tend to zero as the reagent concentration is diminished over the range of our experiments.

The pyridine reaction, even when it starts rapidly, is soon going relatively slowly, usually at considerably less than one-fifth of its initial rate after one-fifth of its realisable course. Such strong retardations must signify back-conversion of a low-concentration intermediate by an accumulating final product, in our case back-conversion of the *tert.*-butyl carbonium ion by the formed bromide ion. This identification of the effect as the common-ion retardation characteristic of the unimolecular mechanism, was confirmed by experiments in which bromide ions were introduced initially as tetramethylammonium bromide: the

FIG. 1. *Reaction of methyl iodide with pyridine in sulphur dioxide at* −15·03°: *initial specific rates, expressed in terms of the electrical conductance, plotted against the concentrations of pyridine.*

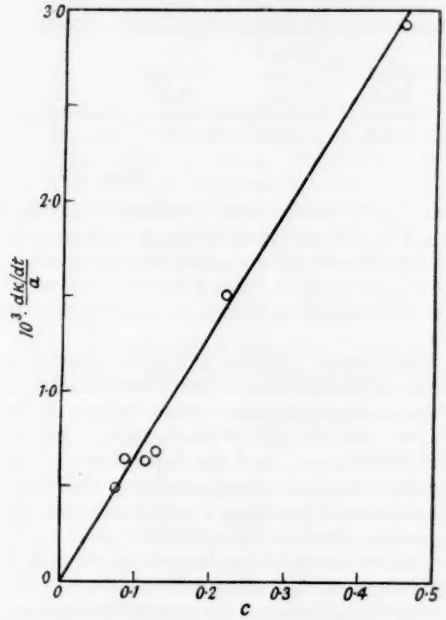
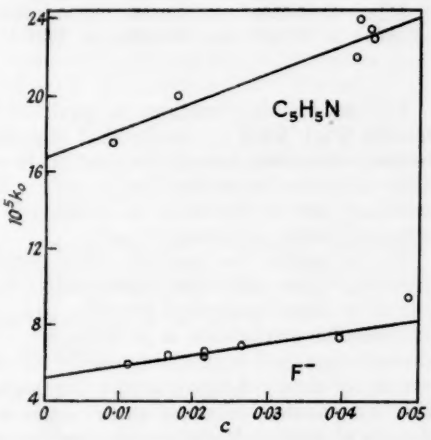


FIG. 2. *Reactions of* tert.*-butyl bromide with fluoride ion and with pyridine in sulphur dioxide at* −15·03°: *initial specific rates* (k_0 *in sec.*$^{-1}$) *of reaction of the alkyl halide plotted against the concentration* (*c in mole*/*l.*) *of the reagent.*



initial rates were then strongly reduced; while further retardation of the continuing reaction became milder than the retardations observed in the absence of added bromide ion.

The definite result obtained in this most highly diagnostic of known tests for the unimolecular mechanism justifies us in regarding the reaction of *tert.*-butyl bromide with pyridine in sulphur dioxide as essentially unimolecular, even though we may later add qualifications of detail to our description:

$$Bu^tBr + C_5H_5N \underset{(2)}{\overset{(1)}{\rightleftharpoons}} Bu^{t+} + Br^- + C_5H_5N \begin{cases} \xrightarrow{(3)} Bu^tNC_5H_5^+ + Br^- \quad . \quad . \quad . \quad (S_N1) \\ \xrightarrow{(3')} C_4H_8 + HNC_5H_5^+ + Br^- \quad . \quad (E1) \end{cases}$$

In this formulation, allowance is made for both substitution and elimination, since both are obviously possible. Actually the only final products which we could find were those of the elimination process; but the possibility is not excluded that they may have arisen by a final fast elimination from a previously formed substitution product, the *tert.*-butylpyridinium ion. In any event the rate would be controlled by step (1). We formed the impression

that the overall reaction was reversible, and appreciably incomplete in our conditions, but, for the reasons mentioned in Part XXXVI, we were not able to determine equilibrium constants.

The initial specific rates of some runs in which tetramethylammonium bromide was initially added are given in Table 3. The factors f, by which the rate is reduced by the added salt, when present in a concentration ρ times that of the pyridine, allow us to estimate, by means of the equation $\alpha = (f^{-1} - 1)/\rho$, the retardation constant α, that is, the ratio of the specific rate of step (2) of the reaction scheme written above, to the sum of the specific rates of steps (3) and (3′). From these figures, and the analogous results recorded in Table 2 of the preceding paper (p. 645), we may conclude that the rates with which fluoride ion, bromide ion, and pyridine combine with the pre-formed *tert.*-butyl carbonium ion in sulphur dioxide diminish in the order of naming, and for our conditions stand to one another as the reciprocals of the numbers, 0·30, 1·0, and 25 respectively.

TABLE 3. *Initial specific rates* ($k_0^{(b)}$ *in sec.*$^{-1}$) *of reaction of* tert.*-butyl bromide with pyridine in the presence of tetramethylammonium bromide in sulphur dioxide at* −15·03°.

No.	[Bu^{t}Br]	[C_5H_5N]	[NMe_4Br]	ρ	$10^5k_0^{(b)}$	f	α
109	0·0314	0·0417	0·0088	0·231	3·1	0·135	27
110	0·0348	0·0434	0·0217	0·500	2·1	0·091	20
111	0·0339	0·0438	0·0015	0·034	12·0	0·52	27
112	0·0340	0·0862	0·0063	0·073	6·5	0·35	25
							Mean = 25

Just as for the reactions of pyridine and triethylamine with *m*-chlorobenzhydryl chloride (Part XXXVI), so for that of pyridine with *tert.*-butyl bromide, it appears that the observed kinetic form is described fairly well, though not quite exactly, by the equation of the unimolecular mechanism (*loc. cit.*). This is illustrated in Table 4 below. The small deviations may be due either to unreality in the idealisations of theory, or, conceivably, to some systematic experimental error.

To summarise, the reaction of *tert.*-butyl bromide with pyridine in sulphur dioxide is kinetically quite unlike the corresponding reaction of methyl iodide, but is very similar to that of *m*-chlorobenzhydryl chloride. The common-ion retardation, characteristic of the unimolecular mechanism, is pronounced. Yet the absolute rate depends slightly on the concentration, and appreciably on the nature of the reagent; and the dependence of the rate on the nature of the reagent is only slightly sensitive to the concentration of the latter. This is a paradoxical situation for single or simultaneous reactions composed exclusively of steps of integral kinetic order; and the suggestion, made in Part XXXVI, may apply here, namely, that, when the unimolecular mechanism is nearly breaking down for lack in the solvent of a sufficiently outstanding power of solvation, then many individual molecular acts of conversion are assisted in varying degrees by the presence of the reagent, though few if any may employ that intimate and specific co-operation which is associated with the bimolecular mechanism.

EXPERIMENTAL

In general, the procedure described in Part XXXVI was followed, and it is therefore necessary only to mention the differences. In the reaction of methyl iodide, the conductance readings were not calibrated to give concentrations. In the reaction of *tert.*-butyl bromide, they were so calibrated, on the assumption that pyridinium bromide was the only reaction product which caused the changes of conductance. In constructing calibration curves, the pyridinium bromide was introduced directly in concentrations determined by weighing. The values of the conversion factor $\Delta x/\Delta\kappa$ varied from 11·5 mole ohm cm.$^{-1}$ at the dilute end of our concentration range to more than twice that value at our highest concentrations.

The initial specific rates of the reaction of methyl iodide with pyridine are in Table 1, and those of the reaction of *tert.*-butyl bromide with pyridine are in Tables 2 and 3. The proportions of the methyl iodide reaction which could be followed were so small that the conductance–time curves were straight lines, which need not be illustrated. The corresponding graphs for the *tert.*-butyl bromide reaction were strongly curved, especially near the beginning of reaction. The course of one of these runs is recorded in Table 4, from which a diagram could be constructed,

having the same general appearance as Fig. 2 of Part XXXVI (p. 639), except that now the experimental points run slightly off the unimolecular curve toward its concave, instead of its convex, side. The Table itself illustrates the much stronger curvature in these reactions than,

TABLE 4. *Illustrating the kinetic course of the reaction of* tert.*-butyl bromide with pyridine in sulphur dioxide at* −15·03° (*run* 106).

Initially, $a = [Bu^tBr] = 0{\cdot}0324$ and $c = [C_5H_5N] = 0{\cdot}0432$. The product concentration is x (M) at time t (sec.). The second-order constants (k_2 in sec.$^{-1}$ mole^{-1} l.) are the calculated values of $\{1/t(c-a)\} \ln \{a(c-x)/c(a-x)\}$, whilst the unimolecular constants (k_1 in sec.$^{-1}$) are computed with $\alpha = 25$ from the equation given on p. 635 of Part XXXVI.

t	10^4x	$10^3x/a$	10^4k_2	10^5k_1		10^4x	$10^3x/a$	10^4k_2	10^5k_1
101	6·4	1·9	47	21·8	600	22·0	6·6	28	18·8
130	8·0	2·4	46	22·6	900	28·0	8·4	24	18·3
164	8·8	2·6	41	21·0	1200	34·0	10·2	22	17·7
180	10·1	3·0	41	21·2	1500	39·0	10·7	20	17·7
243	12·1	3·6	40	20·8	1800	43·0	13·0	19	17·9
300	14·0	4·2	35	19·7	2400	51·0	15·3	16	17·9
420	16·5	5·0	30	18·4					

Mean of first five values = 21·5
Initial value from graph = 23·0

for example, in second-order reactions, by the column of calculated second-order rate constants, which drop to one-half of their initial value after 10% of reaction; calculated first-order rate constants would, of course, drop faster. The moderate success of the general unimolecular equation in describing these reactions is illustrated in the last column of the Table by the rate-constants calculated on this basis.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, GOWER ST., LONDON, W.C.1.

[*Received, October 15th*, 1953.]

The Preparation of Bis-2-cyanoethyl Derivatives of Aromatic Primary Amines, and their Conversion into 1 : 6*-Diketojulolidines. Part III.**

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

[Reprint Order No. 4740.]

The properties of various nuclear-substituted 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines have been studied, particularly their hydrolysis to the corresponding 1-2′-carboxyethyl derivatives and the possibility of decarboxylating the latter to the 1-ethyl derivatives. Although this type of decarboxylation has not been achieved, several other reactions have been elucidated.

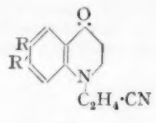
NN-Bis-2-cyanoethylaniline is converted by nitric acid under varying conditions into *NN*-bis-2-cyanoethyl-2 : 4-dinitroaniline, and into *NNN′N′*-tetrakis-2-cyanoethylbenzidine and its 3 : 5 : 3′ : 5′-tetranitro-derivative.

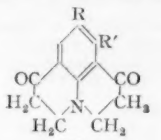
IN Parts I and II (Braunholtz and Mann, *J.*, 1952, 3046; 1953, 1817) we described the cyclisation of nuclear-substituted derivatives of *NN*-bis-2-cyanoethylaniline, $Ph{\cdot}N(C_2H_4{\cdot}CN)_2$, whereby mono- and/or di-cyclisation may occur, to give the corresponding derivatives of 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline (as I) and of 1 : 6-dioxojulolidine (as II). We have now further studied the derivatives of type (I), in order to investigate the possibility (mentioned in Part I) that hydrolysis of the 2-cyanoethyl group followed by decarboxylation might give the corresponding 1-ethyltetrahydro-4-oxoquinolines, and thus provide a synthesis of these 1-alkyl-4-oxo-derivatives alternative to that recently described by Allison, Braunholtz, and Mann (*J.*, 1954, 403). Although these attempts have failed, several noteworthy properties of the intermediate compounds have been revealed.

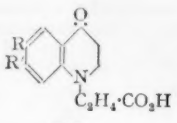
The ratio of the mono- (I) to di-ketone (II) formed on cyclisation of the bis-2-cyano-

* Part II, *J.*, 1953, 1817.

ethylaniline varies considerably with the conditions employed. We have shown (Part II) that *p*-chloro-*NN*-bis-2-cyanoethylaniline when heated with aluminium chloride (8·75 mols.) in chlorobenzene with hydrochloric acid at 155° for 8 hours gives 6-chloro-1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline (I; R = Cl, R′ = H) in 40% yield, no diketone being isolated. Repetition of this experiment, but with aluminium chloride


(I)

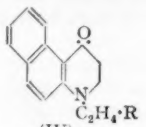

(II)

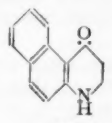

(III)

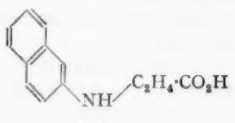
(6·1 mols.) at 170°, gave this monoketone in 74% yield, and 8-chloro-1 : 6-dioxojulolidine (II; R = Cl, R′ = H) in 6·5% yield. The use of *o*-dichlorobenzene as a solvent, with heating at 190—195° for 3·5 hours, gave solely the diketone in 50% yield.

Bis-2-cyanoethyl-*m*-toluidine, however, when similarly heated with the chloride (6 mols.) in chlorobenzene at 150° for 9 hours, gave 7-methyl-1 : 6-dioxojulolidine (II; R = H, R′ = Me) in *ca.* 40% yield, but when heated at 170° for 8·5 hours gave 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-7-methyl-4-oxoquinoline (I; R = H, R′ = Me) in 29% yield and the diketone in 19% yield. Reduction in the proportion of aluminium chloride or the use of *o*-dichlorobenzene as a solvent again gave solely the diketone. In this case in particular, the precise conditions which determine the proportion and yield of the mono- and the di-ketone remain uncertain : it is possible however that the nature of the product is determined primarily by the stability of an intermediate aluminium chloride complex, which may vary considerably under different conditions. (It is assumed that the last monocyclisation has occurred to give the 7-methyl compound, since the formation of the 5-methyl isomer would involve cyclisation on to a carbon atom sterically protected by two *ortho* substituents. The product, m. p. 114·5°, showed no indication of being other than homogeneous. It must be emphasised, however, that no decisive evidence for the position of the methyl group is available.)

The 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines of type (I) underwent smooth alkaline hydrolysis to the corresponding crystalline 1-2′-carboxyethyl derivatives of type (III). With one exception, these acids, like the parent nitriles, could be distilled or sublimed without change. When however 1-2′-cyanoethyl- or 1-2′-carboxyethyl-1 : 2 : 3 : 4-tetrahydro-4-oxo-5 : 6-benzoquinoline (IV; R = CN or CO_2H) was heated under reduced pressure, loss of the side-chain occurred, with the formation of 1 : 2 : 3 : 4-


(IV)


(V)


(VI)

tetrahydro-4-oxo-5 : 6-benzoquinoline (V), the identity of which was confirmed by the fact that its infra-red spectrum showed bands at 3·1 and 6·2 μ corresponding to the :NH and :CO groups respectively. The compound (V) in ethanol showed the following ultra-violet spectrum (λ in mμ), which is almost identical with that of the parent nitrile (IV; R = CN) (cf. Part II) :

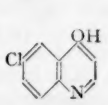
$\lambda_{max.}$	395—396	315	258	216	$\lambda_{min.}$	340	297	236
$\varepsilon_{max.}$	5700	4900	36,600	25,900	$\varepsilon_{min.}$	1050	3700	13,700

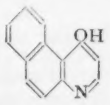
This loss of the side-chain also occurs when the monoketones of type (I) are subjected to acidic hydrolysis. Thus when solutions of the 6-chloro- and the 7-methyl derivative (I; R = Cl, R′ = H; R = H, R′ = Me) in hydrochloric acid were boiled under reflux, the corresponding 6-chloro- and 7-methyl derivatives of tetrahydro-4-oxoquinoline were ultimately isolated. Again the 5 : 6-benzo-analogues formed an exception, for the com-

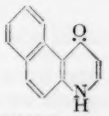
pounds (IV; R = CN and CO_2H) when similarly treated furnished β-2-naphthylaminopropionic acid (VI), the hydrogenated keto-pyridine ring having undergone fission. It is clear that the 2-carboxyethyl group in (VI) is derived from this pyridine ring and not from the original 2′-cyanoethyl or 2′-carboxyethyl group in (IV), because the ketone (V) when similarly treated with hydrochloric acid also gave the acid (VI).

The 6-chloro-acid (III; R = Cl, R′ = H), when heated with copper bronze in quinoline at 235—240°, also lost the side-chain to give the 6-chlorotetrahydro-4-oxoquinoline.

Decarboxylation by pyrolysis of silver salts has been recorded by various authors (cf. Bamberger and Frew, *Ber.*, 1894, **27**, 206; Yu Kanevskaya, Shemyakin, and Bandas, *Ber.*, 1934, **67**, 1518; 1936, **69**, 257, 2152). We found however that the silver salt of the 6-chloro-acid (III; R = Cl, R = H) when heated under reduced pressure gave 6-chloro-4-hydroxyquinoline (VII), and the silver salt of the acid (IV; R = CO_2H) similarly gave 4-hydroxy-5 : 6-benzoquinoline (VIII).


(VII)


(VIII)


(VIII*A*)

Attempted decarboxylation of acids of type (III) by heating them with soda-lime or baryta under reduced pressure gave sublimates in minute yield and was therefore unsatisfactory. The acid (IV; R = CO_2H) gave 5 : 6-benzoquinoline; it is noteworthy that this acid has thus under various conditions given rise to four degradation products. Attempts to prepare the 1-ethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinolines from monoketones of type (I) were therefore abandoned.

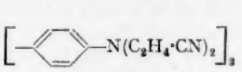
4-Hydroxy-5 : 6-benzoquinoline (VIII) could clearly exist alternatively as the 1 : 4-dihydro-4-oxobenzoquinoline (VIII*A*). Ewing and Steck (*J. Amer. Chem. Soc.*, 1946, **68**, 2181) have found that the ultra-violet absorption spectra of 4-hydroxyquinoline (and several related compounds) in neutral and alkaline solution are almost identical, but differ from that in acid solution : they deduce from this evidence that their compounds in neutral solution exist in the 4-oxoquinoline form (as VIII*A*). The following Table (λ in mμ) shows that the same relation exists between the spectra of the 5 : 6-benzo-derivative in the three media.

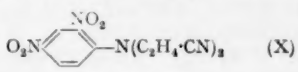
Spectra of 4-*hydroxy*-5 : 6-*benzoquinoline.*

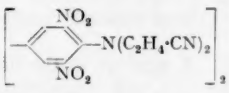
(*A*) in EtOH; (*B*) in aq. 0·1N-NaOH; (*C*) in aq. 0·1N-HCl.

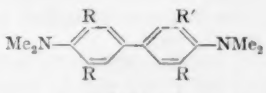
(*A*)	$\lambda_{max.}$	348	332	297	273		$\lambda_{min.}$	339	324	293	241
	$\varepsilon_{max.}$	4050	3840	10,000	39,400		$\varepsilon_{min.}$	2250	2400	9,000	9,750
(*B*)	λ_{max}	348	331	299	274	255	$\lambda_{min.}$	342	326	294	259	238
	$\varepsilon_{max.}$	1690	2100	9,290	32,100	23,300	$\varepsilon_{min.}$	1170	1760	8,670	22,400	14,000
(*C*)	$\lambda_{max.}$	344	312	266	237	213	$\lambda_{min.}$	388	290	250	224	
	$\varepsilon_{max.}$	3470	7270	27,400	25,400	33,700	$\varepsilon_{min.}$	2850	5450	14,600	18,900	

We have investigated the nitration of bis-2-cyanoethylaniline, in order to insert further substituents into this compound and thus into its cyclised derivatives. This compound, when treated in a sulphuric–acetic acid solution with fuming nitric acid, gives *NNN′N′*-tetrakis-2-cyanoethylbenzidine (IX). With concentrated nitric acid, however, it gives

(IX) 


(X)

(XI) 


(XII)

NN-bis-2-cyanoethyl-2 : 4-dinitroaniline (X) and *NNN′N′*-tetrakis-2-cyanoethyl-3 : 5 : 3′ : 5′-tetranitrobenzidine (XI). This behaviour is analogous to that of dimethyl-

aniline, which with oxidising agents gives *NNN'N'*-tetramethylbenzidine (cf. Michler and Pattinson, *Ber.*, 1881, **14**, 2161; Willstätter and Kalb, *Ber.*, 1904, **37**, 3765; Rumpf, *Bull. Soc. chim.*, 1940, **7**, 634) and with nitric acid gives 2 : 4-dinitrodimethylaniline and *NNN'N'*-tetramethyl-3 : 5 : 3' : 5'-tetranitrobenzidine (XII; R = R' = NO_2) (Hodgson, *J.*, 1942, 584; *J. Soc. Dyers and Colourists*, 1944, **60**, 151).

The identities of (IX) and (X) are confirmed by the fact that the ultra-violet spectrum of (IX) closely resembles those of benzidine and *NN'*-bis-2-cyanoethylbenzidine (cf. Part II), whilst that of (X) resembles that of dimethyl-2 : 4-dinitroaniline:

Absorption spectra in ethanol (λ *in* mμ).

Benzidine	$\lambda_{max.}$	283—285	$\varepsilon_{max.}$	26,300	$\lambda_{min.}$	240	$\varepsilon_{min.}$	3160
NN'-Bis-2-cyanoethylbenzidine	$\lambda_{max.}$	296—298	$\varepsilon_{max.}$	26,900	$\lambda_{min.}$	246	$\varepsilon_{min.}$	2690
(IX)	$\lambda_{max.}$	303	$\varepsilon_{max.}$	34,380	$\lambda_{min.}$	244	$\varepsilon_{min.}$	1788
Dimethyl-2:4-dinitroaniline* ...	$\lambda_{max.}$	347	$\lambda_{min.}$	285	$\lambda_{infl.}$	*ca.* 270		
(X)	$\lambda_{max.}$	348—349	$\varepsilon_{max.}$	11,300	$\lambda_{min.}$	286	$\varepsilon_{min.}$	2300
			$\lambda_{infl.}$	268—270	$\varepsilon_{infl.}$	3170		

* Values derived from results of Morgan, Moss, and Porter, *J.*, 1915, **107**, 1296.

The absorption spectrum of the tetranitro-derivative (XI) is unexpectedly simple: this may be due to steric interference between the bis-2-cyanoethylamino- and the nitro-groups, for the dimethylamino-analogue (XII; R = R' = NO_2) shows a similar but less marked effect. Whilst preparing the latter, we have also isolated the scarlet *NNN'N'*-tetramethyl-3 : 5 : 3'-trinitrobenzidine (XII; R = NO_2, R' = H), which gives an orange-yellow solution in methanol. The absorption spectra of these compounds in methanol are given below, ε values being inserted in parentheses and λ being in mμ:

(XI)	$\lambda_{infl.}$	284—293 (13,700)
(XII; R = R' = NO_2)	$\lambda_{max.}$	378 (8170), 365 (8470), 309—310 (23,900)
	$\lambda_{min.}$	373 (7880), 364 (8330), 266 (9890)
	$\lambda_{infl.}$	368—372 (8330), 358—360 (8550), 228—232 (21,600)
(XII; R = NO_2, R' = H)	λ_{max}	418 (5150), 393 (5540), 378 (5770), 315 (25,600)
	$\lambda_{min.}$	414 (4920), 391 (5190), 374 (5650), 267 (11,000)
	$\lambda_{infl.}$	426—432 (4540), 380—384 (5600), 370—372 (5730)

It will be seen that the spectra of the two compounds of type (XII) contain a number of very weak bands, some of which are little more than pronounced inflexions: these two spectra are closely similar in shape, and bear a general resemblance to that of (XI).

The above reactions of bis-2-cyanoethylaniline with nitric acid are of value because the direct dicyanoethylation of nitroanilines or the tetracyanoethylation of benzidine has not yet been achieved.

When this investigation was almost complete, a brief record of the monocyclisation of bis-2-cyanoethylaniline was published by Johnson and DeAcetis (*J. Amer. Chem. Soc.*, 1953, **75**, 2766).

Experimental

Cyanoethylation.—(1) A mixture of *m*-nitroaniline (27 g.), vinyl cyanide (26 c.c., 2·04 mols.), acetic acid (25 c.c., 2·1 mols.), and cuprous chloride (2 g.) was boiled under reflux for 13 hr., allowed to cool, and then poured with stirring into an excess of aqueous ammonia (*d* 0·88). The semi-solid deposit, when recrystallised from ethanol, gave orange **N**-2-*cyanoethyl*-m-*nitroaniline*, m. p. 97·5° (26 g., 70%) (Found: C, 56·45; H, 4·9; N, 22·0. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·8; N, 22·0%).

(2) β-Naphthylamine (5 g.), similarly treated with vinyl cyanide (2·4 c.c., 1·04 mols.), acetic acid (2·1 c.c., 0·95 mol.), and cuprous chloride (0·2 g.) but with 4 hours' heating, gave *N*-2-cyanoethyl-β-naphthylamine, m. p. 99—100° (from ethanol) (Found: N, 14·3. Calc. for $C_{13}H_{12}N_2$: N, 14·3%). Bauer, Cymerman, and Sheldon (*J.*, 1951, 3312) give m. p. 102°.

(3) *p*-Chloroaniline, when cyanoethylated as described in Part II but with 18 hours' heating, gave *p*-chloro-*NN*-bis-2-cyanoethylaniline, m. p. 91—92° (from ethanol), without intermediate distillation, and in 27% yield.

Cyclisation.—(1) p-*Chloro*-**NN**-*bis*-2-*cyanoethylaniline*. A mixture of the dinitrile (11·5 g.), aluminium chloride (40 g., 6·1 mols.), chlorobenzene (30 c.c.), and concentrated hydrochloric acid (1·5 c.c.) was heated at 170° for 8 hr. Working up as previously described (Part II) gave a yellowish-brown oil which rapidly solidified and on fractional crystallisation from ethanol

furnished 6-chloro-1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline (I; R = Cl, R′ = H), pale yellow plates, m. p. 136—137° (8·5 g., 74%), and 8-*chloro*-1 : 6-*dioxojulolidine* (II; R = Cl; R′ = H), brilliant yellow plates, m. p. 200—201° (0·75 g., 6·5%) (Found: C, 60·8; H, 4·2; N, 6·2. $C_{12}H_{10}O_2NCl$ requires C, 61·1; H, 4·25; N, 5·95%); the latter gave a *bisphenylhydrazone*, bright yellow, m. p. 283° (decomp.; in sealed tube) (Found: C, 69·4; H, 5·6; N, 16·6. $C_{24}H_{22}N_5Cl$ requires C, 69·35; H, 5·35; N, 16·85%).

Repetition of the cyclisation using *o*-dichlorobenzene, with heating at 190—195° for 3·5 hours, gave solely the diketone, m. p. 195—197° after one recrystallisation (5·75 g., 50%).

(2) NN-*Bis*-2-*cyanoethyl*-m-*toluidine*. The cyclisation with aluminium chloride (6 mols.) and 9 hours' heating at 150° to 7-methyl-1 : 6-dioxojulolidine (II; R = H; R′ = Me) in 35—45% yield has been described (Part I). Repetition of this experiment, with the dinitrile (10·5 g.) and aluminium chloride (40 g., 6·2 mols.) in chlorobenzene (30 c.c.) containing concentrated hydrochloric acid (1·5 c.c.), and heating at 170° for 8·5 hr., gave a crude product which on fractional crystallisation from ethanol gave the less soluble 1-2′-*cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-7-*methyl*-4-*oxoquinoline* (I; R = H, R′ = Me) (3 g., 29%), very pale yellow, m. p. 114·5° (Found: C, 72·9; H, 6·9; N, 13·15. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·6; N, 13·1%). This gave a *semicarbazone*, colourless needles, m. p. 207°, from aqueous ethanol (Found: C, 62·1; H, 6·0; N, 26·0. $C_{14}H_{17}ON_5$ requires C, 62·0; H, 6·3; N, 25·8%). The ethanolic mother-liquors from the cyclisation ultimately gave the above diketone, m. p. 116—118° (2 g., 19%). When this experiment was modified by using (*a*) treble the above quantities, (*b*) the above quantities but with the chloride reduced to 20 g. (3 mols.), and (*c*) the above quantities with *o*-dichlorobenzene as solvent and with heating at 190—195° for 4 hr., only the diketone was isolated, in yields of 46, 45, and 70% respectively.

(3) NN-*Bis*-2′-*cyanoethyl*-3 : 4-*dimethylaniline*. A mixture of this dinitrile (2 g.), aluminium chloride (7 g., 6 mols.), chlorobenzene (5·5 c.c.), and hydrochloric acid (0·5 c.c.) was heated at 170° for 8·5 hr. The product, worked up as usual, furnished 1-2′-*cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethyl*-4-*oxoquinoline* (I; R = R′ = Me), very pale, yellow plates, m. p. 144·5—145° (from ethanol) (Found: C, 73·6; H, 7·0; N, 12·1. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·05; N, 12·3%): 0·7 g., 35%. It gave a colourless *semicarbazone*, m. p. 216·5°, from aqueous ethanol (Found: C, 63·1; H, 6·7; N, 24·3. $C_{15}H_{19}ON_5$ requires C, 63·1; H, 6·7; N, 24·5%). It is again assumed that the methyl groups are in the 6 : 7- and not the 5 : 6-positions.

Hydrolysis of Nitriles (I) *to Acids* (III).—(1) A solution of the 6-chloro-ketone (I; R = Cl, R′ = H) (8 g.) and potassium hydroxide (10 g.) in aqueous ethanol (50 c.c.) was boiled under reflux for 4 hr., cooled, diluted with water (50 c.c.), filtered, and acidified. The 1-2′-*carboxyethyl*-6-*chloro*-1 : 2 : 3 : 4-*tetrahydro*-4-*oxoquinoline* (III; R = Cl, R′ = H) (7 g., 81%) which separated formed pale yellow crystals, m. p. 154—155°, after repeated recrystallisation from aqueous ethanol (Found: C, 57·0; H, 4·9; N, 5·7. $C_{12}H_{12}O_3NCl$ requires C, 56·8; H, 4·8; N, 5·5%). More concentrated alkali, or longer heating, caused contamination of the acid by a brown tar. The acid gave a pale yellow *silver* salt, m. p. 135° (decomp.) (Found: N, 4·4. $C_{12}H_{11}O_3NClAg$ requires N, 3·9%).

(2) The 7-*methyl* analogue (III; R = H, R′ = Me) was similarly prepared and purified, and furnished almost colourless crystals (77%), m. p. 140·5—142·5° (Found: C, 67·2; H, 6·8; N, 5·9. $C_{13}H_{15}O_3N$ requires C, 66·95; H, 6·5; N, 6·0%).

(3) The 5 : 6-*benzo*-analogue (IV; R = CO_2H), similarly prepared, formed yellow crystals (93%), m. p. 161—161·5° (Found: C, 71·4; H, 5·7; N, 5·15. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6; N, 5·2°). It gave a pale yellow *silver* salt, m. p. 158·5° (decomp.) (Found: N, 3·9. $C_{16}H_{14}O_3NAg$ requires N, 3·7%).

Action of Heat.—(1) The keto-nitriles (I; R = Cl, R′ = H; R = MeO, R′ = H; and R = H, R′ = Me), when heated at 0·1 mm. above their m. p.s, distilled or sublimed unchanged. (2) The keto-acids (III; R = Cl, R′ = H) and (I; R = H, R′ = Me) behaved similarly. (3) The benzo-nitrile (IV; R = CN) when heated at 250°/0·1 mm. gave a viscous yellow distillate which solidified, and when recrystallised from aqueous ethanol furnished 1 : 2 : 3 : 4-*tetrahydro*-4-*oxo*-5 : 6-*benzoquinoline* (V), pale yellow needles, m. p. 138°, in almost theoretical yield (Found: C, 78·9; H, 5·8; N, 7·0. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·65; N, 7·1%). The benzo-acid (IV; R = CO_2H) behaved similarly.

The compound (V) gave a 2 : 4-dinitrophenylhydrazone, bright orange needles, m. p. 247° (decomp.), which could not be obtained pure. Neither a semicarbazone nor a benzoyl derivative could be isolated, and cyanoethylation in acetic acid with cuprous chloride could not be achieved.

When dry hydrogen chloride was passed into an acetone solution of (V), the hydrochloride was rapidly precipitated as bright yellow plates; these were unstable to water and to even

mild heating, having in consequence an indefinite m. p. Consistent analytical values could not be obtained. In contrast, 1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline when similarly treated gave the *hydrochloride* as hygroscopic cream-coloured crystals, m. p. 145° (Found: C, 59·1; H, 5·8; N, 7·6. C_9H_9ON,HCl requires C, 58·85; H, 5·5; N, 7·6%): this hydrochloride, although decomposed by water and hot solvents, is thus appreciably more stable than that of (V).

Action of Hydrochloric Acid.—In the following experiments, a mixture of equal volumes of concentrated acid and water was used throughout. (1) A solution of tetrahydro-4-oxoquinoline (1 g.) in the acid (25 c.c.) was boiled under reflux for 4 hr., and then cooled, neutralised to pH 7, and extracted with ether, 80% of the unchanged ketone being recovered.

(2) When 1 : 6-dioxojulolidine was similarly treated, extraction with chloroform furnished unchanged diketone in 60% yield. When the boiling was extended to 17 hr., only a reddish-brown intractable tar was obtained.

(3) The 7-methyl keto-nitrile (I; R = H, R′ = Me) (1 g.) was treated as in (1), the cold acid solution being however basified and extracted with ether. The extract after removal of the solvent gave a residue which, when recrystallised from aqueous ethanol, furnished tetrahydro-7-methyl-4-oxoquinoline, pale yellow, m. p. 100—101° (Found: C, 74·1; H, 6·7. Calc. for $C_{10}H_{11}ON$: C, 74·5; H, 6·9%): 0·45 g., 60%. The position of the methyl group in this compound, as in the parent nitrile, is uncertain: Clemo and Perkin (*J.*, 1925, 2297) prepared a compound, m. p. 109°, which they considered to be this 7-methyl isomer.

The alkaline solution from the ether-extraction was then acidified and extracted with chloroform. Evaporation of the extract gave a residue which, after recrystallisation from aqueous ethanol, gave the carboxy-ketone (III; R = H, R′ = Me) (0·15 g., 14%), m. p. 138—140°, raised to 140—141·5° on admixture with an authentic sample. It is thus reasonably certain that hydrolysis of the nitrile (as I) to the acid (as III) precedes the complete loss of the side-chain. (4) The 6-chloro-keto-nitrile (I; R = Cl; R′ = H) (1 g.) was treated as in (1), and the cold acid solution then brought to pH 4. The yellow-brown solid deposited (0·7 g., 91%), after recrystallisation from aqueous ethanol and then benzene–*cyclo*hexane, gave 6-chloro-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline, pale yellow needles, m. p. 125·5—126° (Found: C, 59·3; H, 4·6; N, 7·8. Calc. for C_9H_8ONCl: C, 59·5; H, 4·45; N, 7·7%). Extending the time of boiling from 4 to 14 hr. gave identical results.

Since however Elderfield and Maggiolo (*J. Amer. Chem. Soc.*, 1949, **71**, 1906) give m. p. 112° (corr.) for this compound and m. p. 125° (corr.) for β-*p*-chloroanilinopropionic acid, which clearly could also arise under the above conditions, the following confirmation of the identity of the ketoquinoline was obtained. (*a*) It formed a 2 : 4-*dinitrophenylhydrazone*, deep red plates, m. p. 282° (decomp.) (Found: N, 19·6. $C_{15}H_{12}O_4N_5Cl$ requires N, 19·4%). (*b*) Its ultra-violet spectrum (*A*) is almost identical with that of the parent keto-nitrile (*B*) (cf. Part II), both determined in ethanol.

(*A*) $\lambda_{max.}$	392	263	237	$\lambda_{min.}$	292	252
$\varepsilon_{max.}$	3990	8790	22,800	$\varepsilon_{min.}$	61	6530
(*B*) $\lambda_{max.}$	392—394	268—269	239	$\lambda_{min.}$	296	252
$\varepsilon_{max.}$	4490	11,270	25,000	$\varepsilon_{min.}$	220	6900

(*c*) *p*-Chloro-*N*-2-cyanoethylaniline was subjected to alkaline hydrolysis (cf. p. 655), and the clear cold solution then brought to pH 5; the highly crystalline β-*p*-chloroanilinopropionic acid separated, having m. p. 121·5° after recrystallisation from aqueous ethanol (Found: C, 53·9; H, 5·1; N, 6·85. Calc. for $C_9H_{10}O_2NCl$: C, 54·1; H, 5·05; N, 7·0%). This m. p. was markedly depressed when the acid was mixed with the above ketoquinoline.

(5) The 5 : 6-benzo-keto-nitrile (IV; R = CN) (0·5 g.) was similarly treated, with 6·5 hours' boiling. The cold reaction mixture, when neutralised to pH 7, deposited a buff-coloured solid (0·28 g., 75%) which, when recrystallised from benzene and then from aqueous ethanol, gave β-2-*naphthylaminopropionic acid* (VI), cream-coloured plates, m. p. 128—128·5° (Found: C, 72·2; H, 5·8; N, 6·4. $C_{13}H_{13}O_2N$ requires C, 72·5; H, 6·1; N, 6·5%). The acid (VI), in almost the same yield, was obtained by similar treatment of the keto-acid (IV; R = CO_2H) and of the unsubstituted ketone (V).

The identity of the acid (VI) was confirmed by its preparation from *N*-2-cyanoethyl-β-naphthylamine, which on alkaline hydrolysis (cf. p. 655) also furnished (VI), m. p. 125°, unchanged by admixture with the previous sample (Found: C, 72·6; H, 6·3%). The acid did not give a benzoyl or toluene-*p*-sulphonyl derivative under the usual Schotten–Baumann conditions.

The infra-red spectrum of (VI) includes bands at 2·98 and 3·77 μ consistent with its structure

as an amino-acid. Furthermore, its ultra-violet spectrum is closely akin to that of β-naphthylamine :

$C_{10}H_7 \cdot NH_2$	$\lambda_{max.}$	340	290	280	237	213	$\lambda_{min.}$	304	288	258	217
	$\varepsilon_{max.}$	2120	4690	6290	55,000	24,000	$\varepsilon_{min.}$	560	4520	3520	18,700
(VI)	$\lambda_{max.}$	346—8	292	282	244	214	$\lambda_{min.}$	309	288	263	221
	$\varepsilon_{max.}$	2460	7940	9290	48,000	29,900	$\varepsilon_{min.}$	800	7590	5300	14,900

Pyrolysis of Silver Salts.—(1) The silver salt (3·5 g.) of the 6-chloro-acid (III; R = Cl, R′ = H) was heated at 220—225°/0·1 mm. in a wide-bore sublimation tube for 1 hr., a highly crystalline sublimate being deposited. This sublimate (1·2 g., 69%), when recrystallised from aqueous ethanol, gave the colourless hemihydrate of 6-chloro-4-hydroxyquinoline (VII), m. p. 261—262° (Found : C, 57·4; H, 3·5; N, 7·65. Calc. for $C_9H_6ONCl,\frac{1}{2}H_2O$: C, 57·4; H, 3·7; N, 7·4%). The compound in aqueous ethanol gave a blood-red colour with ferric chloride, but an attempted preparation of the 2 : 4-dinitrophenylhydrazone failed. Bachmann and and Cooper (*J. Org. Chem.*, 1944, **9**, 302) give m. p. 269° (corr.) for the anhydrous base.

(2) The silver salt (2 g.) of the acid (IV; R = CO_2H) was similarly treated, the temperature rising to 250°/0·1 mm. The crystalline pale yellow sublimate (0·7 g., 67%) when recrystallised from ethanol gave 4-hydroxy-5 : 6-benzoquinoline (VIII), colourless, m. p. 272—273° (in a sealed tube, bath-temp. rising from 255°) (Found : C, 80·0; H, 4·75; N, 7·3. Calc. for $C_{13}H_9ON$: C, 80·0; H, 4·65; N, 7·2%). Mueller and Hamilton (*J. Amer. Chem. Soc.*, 1943, **65**, 1017) give m. p. 286—288°. It gave a *hydrochloride* which separated in colourless needles of indefinite m. p. when a warm methanolic solution was saturated with hydrogen chloride (Found : N, 5·8. $C_{13}H_9ON,HCl$ requires N, 6·0%).

Attempts to prepare the acetyl and toluene-*p*-sulphonyl derivatives failed, but treatment with boiling phosphorus oxychloride gave colourless 4-chloro-5 : 6-benzoquinoline, m. p. 58—60° (from aqueous ethanol) (Found : N, 6·6. Calc. for $C_{13}H_8NCl$: N, 6·55%). Mueller and Hamilton (*loc. cit.*) give m. p. 62—63°.

Action of Barium Hydroxide.—An intimate mixture of the 5 : 6-benzo-acid (IV; R = CO_2H) and a large excess of the hydroxide was heated at 300—320°/0·03 mm. for 5 hr. The very small pale yellow sublimate, m. p. 68—78°, was treated in ethanolic solution with picric acid, and gave 5 : 6-benzoquinoline picrate, yellow crystals (from methanolic acetone), m. p. 250° alone and when mixed with the sample described below (Found : C, 56·1; H, 2·9; N, 13·4. Calc. for $C_{13}H_9N,C_6H_3O_7N_3$: C, 55·9; H, 3·0; N, 13·7%).

To confirm this identification, β-naphthylamine was converted by the Skraup reaction into 5 : 6-benzoquinoline (60% yield), which gave a picrate, m. p. 251—252° (Found : C, 56·2; H, 3·2; N, 13·5%). It also gave a *hydrochloride*, colourless hygroscopic needles, m. p. 230° (decomp.), from ethanolic acetone (Found : C, 72·3; H, 5·1; N, 6·4. $C_{13}H_9N,HCl$ requires C, 72·4; H, 4·7; N, 6·5%). Skraup and Cobenzl (*Monatsh.*, 1883, **4**, 436) record the picrate, m. p. 251—252°, and the hydrochloride dihydrate, the m. p. of which is not stated.

Action of Quinoline.—A suspension of the 6-chloro-acid (III; R = Cl, R′ = H) (2 g.) in quinoline (25 c.c.) containing copper-bronze (0·1 g.) was heated under reflux (bath-temp., 235—240°) for 2 hr. The cold product was poured into water, the quinoline removed by steam-distillation, and the supernatant yellow aqueous layer decanted from a brown tar. From the aqueous layer 6-chloro-1 : 2 : 3 : 4-tetrahydro-4-oxoquinoline (0·1 g., 7%) slowly crystallised, and after recrystallisation from aqueous ethanol formed yellow crystals, m. p. and mixed m. p. 124—125°. Ethanolic extraction (charcoal) of the tarry residue also gave the keto-quinoline (0·5 g., 35%, estimated as the 2 : 4-dinitrophenylhydrazone).

Nitration of NN-*Bis*-2-*cyanoethylaniline.*—(*a*) A solution of the dinitrile (10 g.) in acetic acid (10 c.c.) containing concentrated sulphuric acid (20 c.c.) was cooled to 0—5°, and vigorously stirred whilst fuming nitric acid (2·5 c.c., 1·2 mols.) was added dropwise so that the temperature did not rise above 25°. The mixture was then stirred at room temperature for 30 min. and poured on ice. The deep blackish-green tarry precipitate, when repeatedly recrystallised from acetone–benzene and then from acetone, gave NNN′N′-*tetrakis*-2-*cyanoethylbenzidine* (IX), pale yellow crystals, m. p. 180° (Found : C, 72·9; H, 6·1; N, 21·1. $C_{24}H_{24}N_6$ requires C, 72·8; H, 6·1; N, 21·2%), in small yield. Its low solubility in boiling solvents precluded reliable molecular-weight determinations. Very slight changes in the above conditions produced heavy tars from which the pure (IV) could not be isolated.

(*b*) The powdered dinitrile (10 g.) was slowly added to vigorously stirred concentrated nitric acid (50 c.c.) at room temperature : the mixture, which had become slightly warm, was stirred for 1·5 hr. and then poured on ice-water (*ca.* 25 c.c.). The dark green precipitate was collected,

washed, dried, and extracted first with boiling benzene and then with boiling acetone–benzene. Each extract, when diluted with *cyclo*hexane, deposited an orange-yellow product, m. p. 127—129° (total yield, 8 g., 55%), which after repeated recrystallisation from acetone–benzene gave NN-*bis*-2-*cyanoethyl*-2 : 4-*dinitroaniline* (X), bright orange-yellow, m. p. 134—135° (Found : C, 49·6; H, 3·8; N, 24·0%; *M*, ebullioscopic in acetone, 288. $C_{12}H_{11}O_4N_5$ requires C, 49·8; H, 3·8; N, 24·2%; *M*, 289). It dissolved readily in aqueous sodium hydroxide to give a red solution.

The undissolved residue from the above extraction when recrystallised from acetone gave NNN′N′-*tetrakis*-2-*cyanoethyl*-3 : 5 : 3′ : 5′-*tetranitrobenzidine* (XI) (2 g., 28%), bright orange, m. p. 225·5° (decomp.) (Found : C, 50·25; H, 3·5; N, 24·1%; *M*, ebullioscopic in acetone, 612. $C_{24}H_{20}O_8N_{10}$ requires C, 50·0; H, 3·5; N, 24·3%; *M*, 576). The low solubility of this compound also precluded more accurate molecular-weight determinations.

Nitration of Dimethylaniline.—(*a*) The amine (8·5 g.) was added slowly with vigorous stirring to dilute nitric acid (250 c.c.; *d* 1·11) at −5°. The mixture was kept at −5° for 30 min. and then set aside overnight at room temperature. The brown semi-crystalline product was washed with much boiling ethanol, and the residue (3 g., 20%) when recrystallised from dioxan gave bright orange *NNN′N′*-tetramethyl-3 : 5 : 3′ : 5′-tetranitrobenzidine (XII; R = R′ = NO_2), m. p. 271° (decomp.) (Found : C, 46·0; H, 3·6. Calc. for $C_{16}H_{16}O_8N_6$: C, 45·75; H, 3·8%). The ethanolic extract deposited dimethyl-2 : 4-dinitroaniline on cooling. This method is based on that of van Romburgh (*Rec. Trav. chim.*, 1922, **41**, 38) who gives m. p. 272° for the tetranitro-compound.

(*b*) When however the amine (5 g.) was added slowly to dilute nitric acid (100 c.c.; *d* 1·13) at 5—10° and this temperature was maintained for 2 hr., the mixture being then poured on ice, the product when repeatedly recrystallised from ethanolic–acetone gave NNN′N′-*tetramethyl*-3 : 5 : 3′-*trinitrobenzidine* (XII; R = NO_2, R′ = H), scarlet needles, m. p. 198·5° (Found : C, 51·3; H, 4·5; N, 18·7%; *M*, ebullioscopic in acetone, 355. $C_{16}H_{17}O_6N_5$ requires C, 51·2; H, 4·55; N, 18·7%; *M*, 375), in small yield. Dimethyl-2 : 4-dinitroaniline was also isolated.

We are greatly indebted to Dr. R. N. Haszeldine for help in the spectroscopic work and to Imperial Chemical Industries Limited, Dyestuffs Division, for the gift of intermediate compounds.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 22nd,* 1953.

The Solvolytic Reactions of 2 : 2-*Dimethyl*-1-*phenylpropyl Bromide.*

By I. DOSTROVSKY and DAVID SAMUEL.

[Reprint Order No. 4134]

The solvolysis of 2 : 2-dimethyl-1-phenylpropyl bromide (CMe_3·CHPhBr) in various solvents has been studied. No rearrangement was found in various aqueous and alcoholic solvents, whereas from the product of solvolysis in moist formic acid a small proportion of 2-methyl-3-phenylbut-2-ene containing a rearranged carbon skeleton was isolated. The rôle of the solvent in this rearrangement is discussed. No evidence for the participation of the migrating group in the solvolytic reaction was found.

IN connection with the study of the rôle of neighbouring groups in displacement reactions, Winstein and Morse (*J. Amer. Chem. Soc.*, 1952, **74**, 1133) have discussed the solvolytic reactions of optically active 2 : 2-dimethyl-1-phenylpropyl chloride (CMe_3·CHPhCl) and toluene-*p*-sulphonate. Acetolysis of both these compounds yielded 2 : 2-dimethyl-1-phenylpropyl acetate with an optical activity indicating a small preponderance of inversion in the course of reaction. In addition, in the acetolysis of the optically active chloride a maximum of 4% of inactive rearranged product is formed. From these results they conclude that a bridged structure of the carbonium ion in this rearrangement is improbable.

In the course of an investigation into the mechanism of rearrangements in the *neo*-pentyl system we had examined the solvolysis of 2 : 2-dimethyl-1-phenylpropyl bromide. Winstein and Morse's conclusions are in essential agreement with our own, but a number of points emerge from the additional data presented below which merit further discussion.

The solvolysis of this bromide in aqueous silver nitrate was first examined by Skell and Hauser (*ibid.*, 1942, **64**, 2633), who obtained as products 2 : 2-dimethyl-1-phenylpropanol containing a proportion of an impurity which they assumed to be 2-methyl-3-phenylbutan-2-ol formed by rearrangement. From the depression of the freezing point of the alcohol, they estimated the extent of rearrangement to be not more than 30%. Winstein and Morse (*loc. cit.*) repeated this work, using a purer bromide, and concluded from the small depression of the freezing point of the resulting alcohol that only very little rearrangement had occurred. In the same reaction, using very pure bromide, we have isolated this impurity from the products and identified it as the nitrate of the unrearranged alcohol. In the solvolysis in aqueous silver nitrate no products other than the unrearranged alcohol and its nitrate were found.

No solvolysis could be detected in a pure water suspension of the bromide even after 24 hours' refluxing, presumably owing to the very limited solubility. Solvolysis in aqueous dioxan mixtures of varying proportions (containing a suspension of potassium carbonate) and in 40% aqueous ethanol yielded the unrearranged alcohol only. Solvolysis in 80% aqueous ethanol gave a mixture of the unrearranged alcohol and its ethyl ether.

In moist formic acid containing approximately 1% of water, a mixture of unrearranged alcohol and up to 10% of an olefin, 2-methyl-3-phenylbut-2-ene, containing a rearranged carbon skeleton was obtained. The rate of formation of this olefin was found to be slower than that of liberation of bromide ion.

In order to eliminate the possibilty that the olefin observed in the solvolysis of the bromide in formic acid is due to the action of the acid on the unrearranged alcohol, the action of formic acid, of acidified dioxan, and of acidified 40% ethanol on 2 : 2-dimethyl-1-phenylpropanol was investigated. It was found that, even under conditions more extreme than those obtaining in the solvolysis reactions, no olefin was produced. On the other hand, the rearranged alcohol, 2-methyl-3-phenylbutan-2-ol, in formic acid at 40° yields this olefin at a rate comparable to that found in the solvolysis of 2 : 2-dimethyl-1-phenylpropyl bromide. It thus appears, that the olefin obtained in the formolysis of this bromide results from the loss of water from the rearranged alcohol or from its formate formed in the course of the reaction. Since the solvolytic reaction is unimolecular, it would seem that in formic acid, at least, both unrearranged and rearranged carbonium ions are capable of separate existence.

Further evidence is obtained by a comparison of the rates of solvolysis of the bromide in 40% aqueous ethanol and in moist formic acid, solvents of almost equal ionizing power. Although no rearrangement was found in the first solvent and up to 10% in the second, the rates were almost identical. Thus no acceleration due to rearrangement could be found such as is evident in the rearrangement of 2 : 2 : 2-triphenylethyl chloride (Brown, Hughes, Ingold, and Smith, *Nature*, 1951, **168**, 65). This would indicate the absence of any neighbouring-group effect and of a synartetic ion in the rearrangement of the 1-phenyl-substituted *neo*pentyl system. A similar conclusion was reached by Winstein and Morse (*loc. cit.*) from their study of the acetolysis of the optically active chloride.

In the absence of neighbouring-group effects, the extent of rearrangement occurring in a solvolytic reaction may be expected to depend on the length of life of the carbonium ion in the particular solvent used as compared with the time required for establishment of equilibrium between the various possible forms of the ion. Although the ionizing power of the solvent has a marked effect on the rate of formation of the carbonium ion, it has relatively little effect on the length of its life, as is shown by the difference in extent of rearrangement in solvents of nearly identical ionizing power, such as moist formic acid and 40% ethanol.

On the other hand, the extent of rearrangement increases in the order of the acidity of the solvent: 40% aqueous ethanol < AcOH < $H{\cdot}CO_2H$, *i.e.*, in the inverse order of their nucleophilic power. It seems that the latter property is the controlling factor in the length of life of the carbonium ion. In the rearrangement of 2 : 2-dimethyl-1-phenylpropyl bromide it would appear that the nucleophilic attack by the water in aqueous alcohol on the unrearranged carbonium ion occurs before the latter has an opportunity to undergo rearrangement. As the nucleophilic power of the solvent is decreased (in acetic

and formic acids) the span of life of the carbonium ion is increased, and with it the opportunity to rearrange.

As has been pointed out by various authors (Skell and Hauser, *loc. cit.*; Eliphimoff-Felkin and Tchoubar, *Compt. rend.*, 1950, **231**, 1314), the unrearranged carbonium ion may by stabilized by the accession of electrons from a 1-phenyl group to the positive carbon atom. In those cases where the rearranging group participates in the solvolytic reaction, these electrons may be provided by the nucleophilic action of this group, thereby reducing the stabilizing influence of a 1-phenyl group. This is probably the cause of the considerable rearrangement of 1 : 2 : 2 : 2-tetraphenylethanol to tetraphenylethylene when treated with hydrogen bromide (Skell and Hauser, *loc. cit.*), whereas no rearrangement can be detected with 2 : 2-dimethyl-1-phenylpropanol under the same conditions.

Thus, whilst the body of evidence both kinetic and stereochemical is for the participation of a migrating phenyl group in solvolysis reactions, there are strong indications that when a methyl group migrates, as for example in the *neo*pentyl system, no such mechanism is in operation and both rearranged and unrearranged carbonium ions can exist.

Experimental

All m. p.s are uncorrected.

2 : 2-Dimethyl-1-phenylpropanol, prepared from *tert.*-butylmagnesium chloride and benzaldehyde, and purified *via* its crystalline hydrogen phthalate (m. p. 140—141°), had m. p. 45·0°. The bromide, prepared by the treatment of this alcohol in ether with gaseous hydrogen bromide at 0° and worked up in the usual way, had b. p. 85—86°/3 mm. No rearrangement occurred in the course of preparation, as is shown by the constant first-order rate coefficients obtained for the solvolysis in 80% aqueous ethanol.

2 : 2-*Dimethyl*-1-*phenylpropyl ethyl ether*, prepared from the bromide and sodium ethoxide in absolute alcohol, had b. p. 98—100°/1 mm. (Found: C, 80·7; H, 10·2; OEt, 23·4. $C_{13}H_{20}O$ requires C, 81·2; H, 10·4; OEt, 23·4%).

2 : 2-*Dimethyl*-1-*phenylpropyl nitrate* was prepared from the bromide and silver nitrate in anhydrous ether by Lucas and Hammett's method (*J. Amer. Chem. Soc.*, 1942, **64**, 1928); it had b. p. 83—86°/3 mm., n_D^{20} 1·5160 (Found: C, 62·9; H, 7·0. $C_{11}H_{15}O_3N$ requires C, 63·0; H, 7·2%).

2-Methyl-3-phenylbutan-2-ol, prepared from methylmagnesium iodide and ethyl hydratropate, had b. p. 92—93°/3 mm., m. p. 19°, n_D^{20} 1·5156. When this was refluxed with anhydrous oxalic acid it afforded 2-methyl-3-phenylbut-2-ene (phenyltrimethylethylene), b. p. 190°.

Solvolysis Experiments.—(a) *In aqueous dioxan* (10%, 50%, *and* 90% *by vol.*). In a typical experiment 2 : 2-dimethyl-1-phenylpropyl bromide (2·5 g.) was dissolved in sufficient aqueous dioxan in which potassium carbonate (2 g.) was suspended. After 36 hr.' refluxing the solution was diluted with water and extracted with ether. On drying and distillation of solvents, the product was found to consist entirely of 2 : 2-dimethyl-1-phenylpropanol, m. p. 45°.

(b) *In aqueous ethanol.* In a number of experiments the bromide was dissolved in aqueous ethanol and kept in a thermostat at 25·1° until the reaction was completed. The solution was then diluted with water and extracted with ether, and the ethereal layer dried and fractionally distilled. The products of solvolysis in 40% aqueous ethanol consisted entirely of 2 : 2-dimethyl-1-phenylpropanol, m. p. 45°, but in 80% aqueous ethanol two fractions were obtained: (i) b. p. 99—102°/20 mm., consisting mainly of 2 : 2-dimethyl-1-phenylpropyl ethyl ether (2—3% of the total) (Found: OEt, 20·3%); (ii) b. p. 90—93°/4 mm., consisting of unrearranged alcohol, m. p. 44·5—45°.

(c) *In aqueous silver nitrate.* In a typical experiment the bromide (23 g., 0·11 mole) was shaken overnight at room temperature with a silver nitrate solution (30 g., 0·17 mole, in 100 ml. of distilled water). After separation of precipitated silver bromide, the aqueous solution was extracted with ether, and the extract washed with cold water and dried (Na_2SO_4). After removal of ether, the residue was fractionally distilled. The product had an m. p. varying from 39° to 42° which could not be changed by further fractionation. The crude product was treated with phthalic anhydride and pyridine in a manner essentially similar to that now described by Winstein and Morse (*loc. cit.*), and the hydrogen phthalate of the unrearranged alcohol extracted from the benzene solution with aqueous sodium carbonate. After acidification of the aqueous carbonate layer, the hydrogen phthalate was extracted, dried, and recrystallized from acetic acid. The purified ester was hydrolysed and steam-distilled, yielding pure 2 : 2-dimethyl-1-phenylpropanol, m. p. 45°.

On removal of the solvent from the benzene layer, a residue melting at approximately 25° was obtained which was re-treated (twice) with phthalic anhydride and pyridine. In the final step a mere trace of hydrogen phthalate was extracted. The residue, b. p. 98—100°/4 mm. (Found: C, 63·6; H, 7·1%), had an infra-red spectrum identical with that of 2 : 2-dimethyl-1-phenylpropyl nitrate, prepared as described above.

(d) *In moist formic acid.* The bromide (2·2 g., 0·01 mole) was dissolved in 98% formic acid (10 c.c.) and kept at 25·1° for 20 hr. The solution was then poured into 500 ml. of water and extracted with ether. The extract was washed with sodium carbonate solution and dried (Na_2SO_4). On removal of ether and fractional distillation of the residue, two fractions were obtained: (i) B. p. 187—188°/758 mm., consisting of 2-methyl-3-phenylbut-2-ene (0·15 g.), n_D^{20} 1·5180; oxidation with 5% potassium permanganate solution, steam-distillation, extraction with ether, and fractional distillation afforded acetophenone (2 : 4-dinitrophenylhydrazone, m. p. 249°). (ii) The residue, consisting of 2 : 2-dimethyl-1-phenylpropanol and its formate, was hydrolysed with 0·1N-sodium hydroxide, extracted with ether, and fractionally distilled. Only unchanged alcohol, m. p. 45°, was obtained.

The rate of formation of olefin was estimated from a number of solvolysis experiments conducted at 39·9°. The amount of olefin was determined either by fractional distillation and weighing or by bromine-number determination on the crude product (A.S.T.M. Standards on Petroleum Products, 1950, p. 677).

In the solvolysis of the bromide (0·1M-solution) in 98% formic acid, the evolution of bromide ions was complete in 5 hr., but only a trace of olefin was detected in the mixture after 6 hr. and less than 10% after 24 hr. Under similar conditions, a solution of 2 : 2-dimethyl-1-phenylpropanol gave no olefin fraction even after 36 hr., whilst a solution of 2-methyl-3-phenylbutan-2-ol gave about half the equivalent amount of olefin in the same time. No olefin was detected in the products of the action of 50% aqueous dioxan, 0·12N in perchloric acid, at 100° for 12 hr. on 2 : 2-dimethyl-1-phenylpropanol; pure alcohol (m. p. 44—48°) was recovered unchanged in over 97% yield, care being taken that at no stage in the recovery could fractionation of alcohol and olefin occur. The time of reaction used in this experiment is calculated to be at least 1000 times longer than the time required for the solvolysis of the bromide under the same conditions. No olefin was detected in the action of 40% aqueous ethanol 0·1N in perchloric acid at 25° for 14 hr. on the unrearranged alcohol.

Kinetic Measurements.—Materials. 2 : 2-Dimethyl-1-phenylpropyl bromide was prepared as above. 40% Aqueous ethanol was obtained by mixing 40 vol. of dry ethanol (distilled from CaO) and 60 vol. of distilled water. Formic acid, 98—100% (Baker & Adamson C.P.), was recrystallised four times; the product had m. p. 7·0°, indicating approx. 1% of water.

Measurements. The rate of solvolysis was determined by a conductivity method. Cells were made of Pyrex glass of approximately 8—10 ml. capacity, in the sides of which smooth platinum electrodes were sealed. Solvent was added to a level about 1 cm. above the electrodes, and the cell closed with a ground-glass stopper and immersed for 30 min. in a water-filled thermostat at 25·10° ± 0·03°.

A drop of the bromide was added from a capillary and dissolved by shaking. At measured times the conductivity was determined with a bridge assembly of the type described by Jones and Josephs (*J. Amer. Chem. Soc.*, 1928, **50**, 1049), with a 1300-cycles phase shift audio-oscillator, a peaked audio-amplifier, and head-phones. At the high dilutions used (0·001—0·0001M) it may be assumed that conductivity is proportional to concentration. The first-order rate constants were therefore calculated directly from the conductivities of each run by means of the relation $k_1 = (2{\cdot}3/t) \log (k_\infty - k_0)/(k_\infty - k_t)$, where k_0, k_t, and k_∞ are the reciprocals of resistance at time zero, t, and infinity, respectively.

Satisfactory results were obtained for the solvolysis in 40% aqueous ethanol but a slight upward drift towards the end of the reaction was apparent in formic acid. A similar but larger trend is reported by Evans and Hamann (*Trans. Faraday Soc.*, 1951, **47**, 28). The results are summarized below:

Solvent	"Y" Factor *	$k_1 \times 10^4$ at 25·1°
40% Aqueous ethanol	2·151	5·42
Formic acid	2·08	5·15

* Grunwald and Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

The authors thank Professor E. D. Hughes, F.R.S., for useful comments on the manuscript.

THE WEIZMANN INSTITUTE OF SCIENCE, REHOVOT, ISRAEL. [*Received, March 2nd*, 1953.]

Amino-acids and Peptides. Part XI. The Kinetics of the Self-condensation of Glycylglycylglycine Methyl Ester.*

By P. S. Rees, D. P. Tong, and G. T. Young.

[Reprint Order No. 4652.]

The velocity of the self-condensation of glycylglycylglycine methyl ester in methanol solution to give pentaglycylglycine methyl ester has been measured at 0°, 25°, and 60°. Second-order velocity constants are found, and the activation energy is calculated to be 5·5 kcal./mole. The frequency factor of the Arrhenius equation is 10^{-1} (l. mole^{-1} sec.$^{-1}$), and the entropy of activation is −63 e.u. The possible significance of these abnormally low values is briefly discussed.

Fischer (*Ber.*, 1906, **39**, 471) observed that when solid glycylglycylglycine methyl ester is heated at 100° self-condensation occurs to give pentaglycylglycine methyl ester:

$$2NH_2\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot CO_2Me \longrightarrow NH_2\cdot CH_2\cdot CO\cdot[NH\cdot CH_2\cdot CO]_4\cdot NH\cdot CH_2\cdot CO_2Me + MeOH$$

Pacsu and Wilson (*J. Org. Chem.*, 1942, **7**, 117, 126) noted that the reaction proceeds in methanol solution at room temperature, the hexapeptide ester separating out; they also examined the products obtained by heating solid glycylglycylglycine methyl ester for longer periods, further condensation then occurring. The self-condensation of D-alanylglycylglycine methyl ester was reported by Fischer (*Ber.*, 1906, **39**, 2893), and of its racemate by Pacsu and Wilson (*loc. cit.*), who made similar observations on DL-leucylglycylglycine. Curtius (*Ber.*, 1904, **37**, 1300) had earlier reported that triglycylglycine ethyl ester behaves in an analogous fashion, but Fischer (*loc. cit.*) found no change on heating either the ethyl or the methyl ester of triglycylglycine at 100°. Recently, Sluyterman and his co-workers (*Rec. Trav. chim.*, 1952, **71**, 137, 277) reported that the latter ester gives apparently polymeric products when heated for a long time alone or in methanolic solution at 100°, but in this case and in that of glycylglycylglycine methyl ester they found evidence of *N*-methyl derivatives in the product.

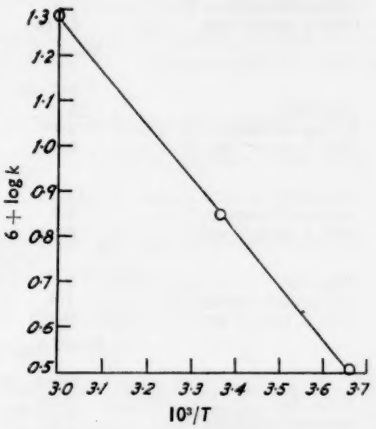
A preliminary examination with N. H. Woodbury (Thesis, Bristol, 1948) suggested that the kinetics of the self-condensation of glycylglycylglycine methyl ester in methanolic solution had interesting and unusual features; the reaction proceeds slowly at room temperature, and yet the temperature coefficient of the velocity appeared to be remarkably low. We now report the results of a detailed investigation of the kinetics of this reaction.

For the first preparation of the starting material, we coupled benzyloxycarbonylglycyl chloride with glycylglycine methyl ester; hydrogenation of the product gave glycylglycylglycine methyl ester hydrochloride, from which the ester was liberated as required by the addition of a calculated amount of sodium methoxide. A more convenient route was adopted later, using the mixed-anhydride method of Wieland and Bernhard (*Annalen*, 1951, **572**, 190), Boissonnas (*Helv. Chim. Acta*, 1951, **34**, 874), and Vaughn and Osato (*J. Amer. Chem. Soc.*, 1951, **73**, 3547). By the action of ethyl chloroformate in the presence of triethylamine, benzyloxycarbonylglycine was coupled with glycine methyl ester; hydrolysis of the product gave benzyloxycarbonylglycylglycine, which was coupled again with glycine methyl ester; the remaining stages are indicated above.

In the initial kinetic studies we took advantage of the insolubility of pentaglycylglycine methyl ester in methanol, and measured the rate of the reaction by weighing the separated product. A more satisfactory procedure was used in the later work; the reaction mixture was added to aqueous boric acid, and the free amino-groups were then titrated with 0·01N-acid. Control experiments showed that under these conditions both glycylglycyl- and pentaglycyl-glycine esters were titrated. The results reported here were obtained by this method. The velocity of the reaction was measured at 25° with three different initial

* Part X, *J.*, 1953, 2481.

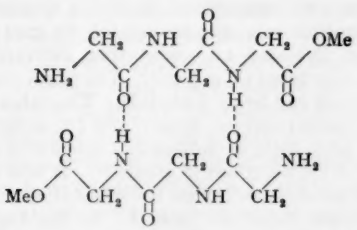
concentrations, and also at 0° and 60°. The prolonged action of boiling methanol on pentaglycylglycine methyl ester failed to yield methanol-soluble products, the reaction being irreversible under these conditions. In view of the work of Sluyterman and his co-workers (*locc. cit.*), a careful examination was made of the hexapeptide ester formed in our experiments. A portion was hydrolysed with hydrochloric acid, and the product was chromatographed on paper, with phenol saturated with water as the mobile phase. With this solvent, sarcosine and glycine are widely separated, and control experiments showed that 1% of sarcosine in glycine could readily be detected. No sarcosine could be found in the hydrolysis product. It may be added that a similar examination of the self-condensation product of triglycylglycine methyl ester in methanol at 60° failed to detect *N*-methylation.



The results of the velocity measurements are shown in Table 1, and it is seen that satisfactory velocity constants are obtained from the second-order equation. The order of the reaction is confirmed by the variation of the time required for partial reaction when the initial concentration is varied (Table 2). From the Arrhenius equation, the energy of activation is calculated to be 5·5 kcal./mole, and the frequency factor A is 10^{-1} (l. mole^{-1} sec.$^{-1}$). From the equation $A = \boldsymbol{RT}e^{\Delta S^*/\boldsymbol{R}}/\boldsymbol{Nh}$ the entropy of activation ΔS^* is calculated to be −63 e.u. Experimental difficulties, particularly at the lower concentrations, prevented the attainment of high accuracy, but there appears to be no doubt of the order of these figures.

The characteristics of this reaction merit some discussion. The frequency factor is very low; Bell (*J.*, 1943, 629) gives the normal range as 10^2—10^7 for second-order organic reactions between uncharged molecules in solution. The correspondingly low entropy of activation must be expected for a reaction which proceeds with measurable rate at normal temperatures with such a small activation energy. Such figures as are available show that the activation energy of the aminolysis of esters is normally considerably higher; Baltzly, Berger, and Rothstein (*J. Amer. Chem. Soc.*, 1950, **72**, 4149) indicate a range of 11—13 kcal./mole, and in experiments to be published we have found an activation energy of *ca.* 14 kcal./mole for the reaction of *cyclo*hexylamine with methyl phenylacetate in methanol. We suggest that the low activation energy of the self-condensation of glycylglycylglycine methyl ester may be due to the intermediate formation of a hydrogen-bonded complex, such as (I), in which the reacting molecules adopt a head-to-tail position; the ester and the amino-groups of the adjoining molecules are held in proximity, and conditions

(I)



would then be favourable for the reaction to be completed by the elimination of methanol. It may be shown that if this hypothesis is correct then in the present case the apparent activation energy would be lower than that for a similar reaction not involving such an intermediate, by an amount equal to the heat of formation of the hydrogen bonds.

A recent paper by Wetzel, Miller, and Day (*J. Amer. Chem. Soc.*, 1953, **75**, 1150) reports low values for the activation energy and activation entropy of the reaction of methyl acetate with ammonia in mixed solvents, but an earlier paper of the same series (Gordon, Miller, and Day, *ibid.*, 1948, **70**, 1946) gives an activation energy of 12·7 ± 2 kcal./mole

TABLE 1.

Temp., 0°. *Initial concn.*, 0·373M.

Time, hr.	19·75	44·0	58·5	82·5
Self-condensation, %	7·8	15·6	19·8	26·2
10^5k, l. mole^{-1} sec.	0·319	0·313	0·313	0·320

Mean, $k_0 = 0{\cdot}32 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

Temp. 25°; (a) *Initial concn.*, 0·0846M.

Time, hr.	23	47	92	158	206	254	300
Self-condensation, %	4·1	8·1	14·2	22·2	27·9	32·6	36·4
10^5k, l. mole^{-1} sec.$^{-1}$	0·604	0·615	0·589	0·596	0·619	0·627	0·628

(b) *Initial concn.*, 0·185M.

Time, hr.	17	38	65	88	102
Self-condensation, %	8·3	16·6	25·9	32·4	35·2
10^5k, l. mole^{-1} sec.$^{-1}$	0·804	0·795	0·812	0·821	0·798

(c) *Initial concn.*, 0·375M.

Time, hr.	2	4·5	8	15·5	23	39·5
Self-condensation, %	1·8	4·1	6·8	12·3	18·2	27·4
10^5k, l. mole^{-1} sec.$^{-1}$	0·687	0·704	0·680	0·671	0·720	0·707

Mean, $k_{25} = 0{\cdot}70 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

Temp., 60°. *Initial concn.*, 0·371M.

Time, hr.	0·75	4·5	8·5	11·0	19·75	24·75	29·0
Self-condensation, %	1·8	9·7	18·4	22·6	35·1	40·2	42·9
10^5k, l. mole^{-1} sec.$^{-1}$	1·88	1·78	1·99	1·99	2·05	2·03	1·94

Mean, $k_{60} = 1{\cdot}95 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$.

under apparently identical conditions, and a clarification of the position must be awaited. We are now examining the behaviour of glycylsarcosylsarcosine methyl ester, in which hydrogen bonding between peptide groups is excluded, and other analogous reactions, and a detailed discussion is postponed until these results are presented.

EXPERIMENTAL

Glycylglycylglycine Methyl Ester.—The free ester was liberated from the hydrochloride immediately before use. To a suspension of the hydrochloride in dry methanol was added methanolic sodium methoxide (0·93 equiv. calculated on the determined chloride content of the salt), the temperature being kept at −5°. The solvent was removed rapidly below 30°, and the residual solid was extracted with warm dry chloroform. The extracts were filtered and most of the chloroform was removed *in vacuo* at room temperature. Dry ether was added, and the crystalline ester was filtered off, washed with ether, and dried in a vacuum-desiccator for 15 min.

Kinetic Measurements.—Procedure. Glycylglycylglycine methyl ester was dissolved in sufficient methanol (dried with magnesium) to give a solution of approximately the required concentration; centrifugation was usually needed to give a clear solution. Approximate volumes of the solution (0·1—0·5 ml.) were then delivered by means of a micropipette into numbered, weighed test-tubes (3 × $\frac{3}{8}$ in.). The tubes were sealed and then weighed again (the weight of the drawn-off end being included). The tubes were placed in a thermostat and at suitable intervals they were removed, broken into 2% aqueous boric acid (5 ml.), and titrated with 0·01N-hydrochloric acid, with, as indicator, 4 drops of a mixture of bromocresol-green and methyl-red (5 : 2 vol. of 0·1% solutions in ethanol). It was sometimes necessary to warm the solutions slightly before titration to hasten the dissolution of pentaglycylglycine methyl ester.

Results. The results are shown in Table 1. At the highest concentration (0·37M), some condensation occurred before the first titration could be made, and the figures recorded have been corrected for the time taken in making up and weighing the solutions, the true initial concentration being obtained by extrapolation. The velocity constants, k, are derived from the second-order equation.

The times for 30% reaction at 25° were obtained graphically from the results recorded

above, and Table 2 shows the apparent order of the reaction, n, calculated from the equation $n = 1 + \frac{\log t_1/t_2}{\log a_2/a_1}$, where t_1 and t_2 are the times for partial reaction at initial concentrations a_1 and a_2 respectively.

TABLE 2.

Initial concn., mole/l.	0·0846	0·375	0·185	0·375
Time for 30% reaction, hr.	225	43	80	43
Apparent order of reaction, n	2·1		1·9	

From the gradient of the graph shown, the Arrhenius equation gives an activation energy of 5·47 kcal./mole, and a frequency factor A of 10^{-1} (l. mole^{-1} sec.$^{-1}$). The corresponding entropy of activation ΔS^* is calculated to be -63 e.u.

We are grateful to Dr. L. A. Woodward and Mr. R. P. Bell for helpful discussions.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, September 15th*, 1953.]

---

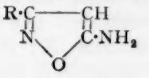
isoOxazolones. *Part VI.* The Hydrogenation of 5-Aminoisooxazoles. A New Synthesis of Pyrimidines.*

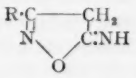
By G. SHAW and (MRS.) G. SUGOWDZ.

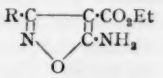
[Reprint Order No. 4701.]

Hydrogenation of 5-amino-3-phenyl*iso*oxazole (I; R = Ph) gave β-aminocinnamamide (V), but the acyl derivatives (VII; R = Ph, Me, and H) gave mixtures of the amines (VIII; R = Ph, Me, and H), and the hydroxypyrimidines (X; R = Ph, Me, and H). The reactions of (VIII), in particular their ready conversion into (X), have been studied.

EARLIER communications in this series have been concerned primarily with a study of the structures and properties of the hydrogenation products of certain *iso*oxazol-5-ones. We have extended this study to the behaviour of analogous *iso*oxazolone imines (I*a*) or tautomeric 5-amino*iso*oxazoles (I) towards hydrogenation; in the present paper we adhere to the latter formulation. A preliminary note on the findings has already appeared (Shaw and Sugowdz, *Nature*, **1953**, **172**, 955).


(I)


(I*a*)

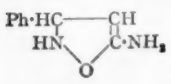

(II)

The only 5-amino*iso*oxazoles studied in any detail are (I; R = Me and Ph), prepared by the reaction of hydroxylamine with a cyanoacetylene (Moureu and Lazennec, *Compt. rend.*, 1907, **144**, 1281; *Bull. Soc. chim.*, 1907, **1**, 1084), a β-aminoacrylonitrile (Burns, *J. pr. Chem.*, 1893, **47**, 123), and a β-oxo-nitrile (Obregia, *Annalen*, 1891, **266**, 329), and more recently the reaction of benzhydroxamoyl chloride and ethyl cyanoacetate was shown to give the ester (II; R = Ph), which was hydrolysed to the acid and then decarboxylated to give (I; R = Ph) (Quilico and Fusco, *Rend. Ist. Lombardo Sci.*, 1936, **69**, 439); we have prepared the analogous ester (II; R = Me) by the reaction of hydroxylamine with ethyl 2-cyano-3-oxobutanoate and similarly converted it into (I; R = Me). In the present work, however, attention has been confined to 5-amino-3-phenyl*iso*oxazole (I; R = Ph), obtained in excellent yield from benzoylacetonitrile and hydroxylamine (Obregia, *loc. cit.*).

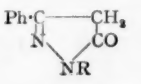
In the presence of Raney nickel or Adams platinum catalyst in ethanol at room temperature the amino*iso*oxazole (I; R = Ph) absorbed only 1 mol. of hydrogen, giving in good yield a crystalline dihydro-compound, provisionally regarded as the *iso*oxazoline (III) by analogy with the products of hydrogenation of *iso*oxazolones (Part II, *J.*, 1017). The compound was basic and formed monoacyl derivatives but with cold dilute acid it was

* Part V, *J.*, 1953, 3467.

rapidly hydrolysed to benzoylacetamide. Condensation of the compound, or its acyl derivatives, with hydrazine and phenylhydrazine in an attempt to prepare amino- or acylamino-pyrazoles, gave in each case only the pyrazolones (IV; R = H and Ph). These



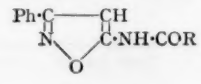
(III)



(IV)

$Ph{\cdot}C(NH_2){:}CH{\cdot}CO{\cdot}NH_2$
(V)

$Ph{\cdot}C(NH{\cdot}COR){:}CH{\cdot}CO{\cdot}NH_2$
(VI)



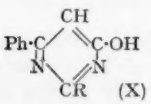
(VII)

results necessitated a revision of the structure of the dihydro-compound which was shown to be β-aminocinnamamide (V) by comparison with a sample prepared in very poor yield from ethyl benzoylacetate and ammonia (Guareschi, *Chem. Zentr.*, 1896, I, 603; 1905, II, 685). The *iso*oxazoline (III) is undoubtedly an intermediate in the formation of the linear compound, and a similar ring opening, following hydrogenation, has been observed with certain *iso*oxazolones (Part V, *loc. cit.*).

5-Acetamido-3-phenyl*iso*oxazole (VII; R = Me) also readily absorbed 1 mol. of hydrogen in the presence of nickel or platinum catalysts, but the product was a mixture from which were isolated three compounds in variable yields; the compounds were (*a*) an amphoteric substance with predominantly basic properties, (*b*) an amphoteric substance which was essentially acidic, and (*c*) a compound which appeared to be a salt of (*a*) and (*b*). The basic substance was very readily hydrolysed by cold dilute acid with loss of ammonia, and further hydrolysis of the product gave benzoylacetamide; in addition the base reacted with hydrazine and phenylhydrazine to give the pyrazolones (IV; R = H and Ph) respectively. These results and the analytical data indicated that the base was *N*-(β-aminocinnamoyl) acetamide (VIII; R = Me) and the first hydrolysis product *N*-(benzoylacetyl)acetamide (IX; R = Me).

$Ph{\cdot}C(NH_2){:}CH{\cdot}CO{\cdot}NH{\cdot}COR$
(VIII)

$Ph{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}COR$
(IX)



(X)

The base (VIII; R = Me) was remarkably labile, and lost a mol. of water when melted, when its aqueous or alcoholic solutions were boiled for a short time, when an aqueous-alcoholic solution was incubated at 35° for a few hours, or when its solution in dilute sodium hydroxide was kept at room temperature for a few minutes. The product in each case was the acidic compound (*b*); this was the hydroxypyrimidine (X; R = Me) (Pinner, *Ber.*, 1889, **22**, 1618). The lability of the base explains the variation in composition of the mixtures obtained by hydrogenation of (VII; R = Me), and when these mixtures were heated with water, or treated with dilute alkali, an almost quantitative yield of the pyrimidine (X; R = Me) resulted.

Similar compounds were obtained by hydrogenation of the *iso*oxazoles (VII; R = H and Ph) although acid hydrolysis of (VIII; R = H) was anomalous in giving a substance $C_9H_7O_2N$ as well as (IX; R = H). The reaction thus provides a method for introducing substituents into the 2-position in the pyrimidine ring in good yield without using amidines which are often not easily accessible and frequently give poor yields. The reaction, in addition, includes a new synthesis of certain diacylamides, notably (VIII) and (IX), and, moreover, suggests other routes to this type of compound from an appropriate heterocyclic amino-compound; these and related problems are being investigated.

Not unexpectedly, when the acyl derivatives (VI; R = Me and Ph) were melted the corresponding pyrimidines (X; R = Me and Ph) were obtained; the compounds (VI) however were much less labile than (VIII) and failed to cyclise in boiling ethanol or water. During a preparation of (VI; R = Ph) from the base (V) and benzoyl chloride in sodium hydroxide solution a small amount of the pyrimidine (X; R = Ph) was isolated, and this prompted an investigation of the action of sodium hydroxide on (VI; R = Ph); surprisingly, cyclisation occurred when a solution of the latter compound in N-sodium hydroxide was warmed for 10 min.

Experimental

Hydrogenations were carried out at room temperature and atmospheric pressure; the recorded volumes of hydrogen refer to N.T.P.

Hydrogenation of 5-Amino-3-phenylisooxazole (I; R = Ph).—The *iso*oxazole, prepared from benzoylacetonitrile and hydroxylamine (Obregia, *loc. cit.*), crystallised from ethanol–water as needles, m. p. 112°; the reaction, when carried out in more concentrated solution than that used by Obregia (*loc. cit.*) gave better yields (80—90%). The *iso*oxazole (2 g.) in ethanol (30 ml.) was reduced with hydrogen and Raney nickel (2 ml.), hydrogen (290 ml. Calc. for 1 mol.: 280 ml.) being absorbed during 3 hr. (less when Adams platinum catalyst was used). Evaporation of the filtered solution *in vacuo* gave a very pale yellow solid; β-aminocinnamamide (1·8 g.) separated from ethanol as needles, m. p. 164° (Found: C, 66·55; H, 6·35; N, 17·0. Calc. for $C_9H_{10}ON_2$: C, 66·65; H, 6·2; N, 17·25%), undepressed when mixed with an authentic specimen, m. p. 164° (Guareschi, *loc. cit.*). The amine (0·5 g.) was warmed with N-hydrochloric acid (6 ml.) and from the clear solution benzoylacetamide (0·4 g.) separated on cooling, and recrystallised from water as needles, m. p. 112—113° (Found: C, 66·25; H, 5·35; N, 8·4. Calc. for $C_9H_9O_2N$: C, 66·25; H, 5·55; N, 8·0%), undepressed when mixed with an authentic specimen, m. p. 112° (Guareschi, *Chem. Zentr.*, 1904, II, 905). A solution of the amine (0·5 g.) in ethanol (10 ml.) containing phenylhydrazine (0·34 g.) was boiled under reflux for 2 hr.; evaporation of the solvent *in vacuo* gave 1 : 3-diphenylpyrazol-5-one (0·5 g.) which crystallised from ethanol as needles, m. p. 136—137° (Found: C, 76·05; H, 5·15; N, 11·95. Calc. for $C_{15}H_{12}ON_2$: C, 76·25; H, 5·1; N, 11·85%). Similarly the amine and hydrazine gave 3-phenylpyrazol-5-one as colourless plates (from ethanol), m. p. 236° (Found: C, 67·5; H, 5·15; N, 14·45. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·05; N, 14·5%); the m. p.s of the pyrazolones were undepressed when mixed with authentic specimens, prepared from ethyl benzoylacetate and the appropriate hydrazine (Knorr and Klotz, *Ber.*, 1887, **20**, 2546; Curtius, *J. pr. Chem.*, 1894, **50**, 515).

β-Acylaminocinnamamides (VI).—β-Aminocinnamamide (1 g.) and acetic anhydride (4 ml.) were warmed together on a water-bath for 15 min.; addition of water to the cooled solution precipitated an oil which soon crystallised; *β-acetamidocinnamamide* (0·8 g.) separated from ethanol–water as colourless needles, m. p. 238—240° (Found: C, 64·7; H, 5·9; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·6; N, 13·7%). The amide (0·1 g.) was melted and the product crystallised from ethanol as colourless needles, m. p. 242—243° (Found: C, 70·7; H, 5·25; N, 15·05. Calc. for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%) undepressed when mixed with 6-hydroxy-2-methyl-4-phenylpyrimidine, m. p. 242° (Pinner, *loc. cit.*). A solution of the amide (0·1 g.) in N-sodium hydroxide (10 ml.) was warmed on a water-bath for 10—15 min., cooled, and neutralised with hydrochloric acid, to give 6-hydroxy-2-methyl-4-phenylpyrimidine (0·06 g.). β-Aminocinnamamide (1 g.) and benzoyl chloride (1·5 g.) were shaken together in 2N-sodium hydroxide (10 ml.), and the precipitate of *β-benzamidocinnamamide* (1·1 g.) crystallised from ethanol as colourless needles, m. p. 216—218° (Found: C, 72·0; H, 5·05; N, 10·25. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%). Acidification of the alkaline filtrate and crystallisation of the precipitate from ethanol gave 6-hydroxy-2 : 4-diphenylpyrimidine (0·1 g.), m. p. and mixed m. p. 289—290° (Found: C, 77·7; H, 4·7; N, 11·0. Calc. for $C_{16}H_{12}ON_2$: C, 77·4; H, 4·85; N, 11·3%) (Pinner, *loc. cit.*; Ruhemann and Stapleton, *J.*, 1900, **77**, 244). The hydroxydiphenylpyrimidine was also obtained from β-benzamidocinnamamide by the action of heat or of sodium hydroxide solution.

5-Formamido-3-phenylisooxazole (VII; R = H).—A solution of 5-amino-3-phenyl*iso*oxazole (2 g.) in formic acid (5 ml. 98%) was warmed to 60° and acetic anhydride (4 ml.) added slowly so that the temperature did not exceed 60°; the solution was kept at 60° for 2 hr., then cooled, and water (20 ml.) was added to precipitate *5-formamido-3-phenylisooxazole hemihydrate* (1·9 g.) which crystallised from water as colourless needles, m. p. 115—117° (decomp.) (Found: C, 60·8; H, 4·35; N, 14·3. $C_{10}H_8O_2N_2,\frac{1}{2}H_2O$ requires C, 60·9; H, 4·6; N, 14·2%). The acetyl (Burns, *loc. cit.*) and benzoyl (Moureu and Lazennec, *loc. cit.*) derivatives were similarly prepared.

Hydrogenation of Acylaminoisooxazoles.—5-Acetamido-3-phenyl*iso*oxazole (1 g.) in ethanol (30 ml.) was hydrogenated over Raney nickel (2 ml.), hydrogen (116 ml. Calc. for 1 mol.: 111 ml.) being absorbed during 6 hr. (1—2 hr. when Adams platinum catalyst was used). Evaporation of the filtered solution *in vacuo* gave a solid mixture which had a wide melting range. The properties of this varied somewhat in different experiments, but rapid crystallisation from ethanol gave *N-β-aminocinnammoylacetamide* (0·3 g.) as prisms, m. p. 136° (decomp.)

(Found: C, 64·65; H, 5·7; N, 13·85. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). From the ethanolic solution 6-hydroxy-2-methyl-4-phenylpyrimidine (0·2 g.) gradually separated; this crystallised from ethanol as needles, m. p. and mixed m. p. 243°. On one occasion, careful evaporation of the last-mentioned ethanolic solution *in vacuo*, and crystallisation of the residue from ethanol, gave a *substance*, possibly a salt of *N*-β-aminocinnamoylacetamide and the hydroxypyrimidine as colourless needles, m. p. 238° (Found: C, 67·2; H, 5·8; N, 14·35. $C_{11}H_{12}O_2N_2,C_{11}H_{10}ON_2$ requires C, 67·7; H, 5·7; N, 14·35%); this was converted into the hydroxypyrimidine when boiled with water. The last hydrogenation was repeated and the solid residue boiled with water (5 ml.) for 2 hr.; the solution was cooled, to give 6-hydroxy-2-methyl-4-phenylpyrimidine (0·8 g.), m. p. and mixed m. p. 238—240°. A solution of *N*-β-aminocinnamoylacetamide (0·5 g.) in N-hydrochloric acid (6 ml.) was warmed for a few min., then cooled, and the precipitate collected; N-(*benzoylacetyl*)*acetamide* (0·3 g.) crystallised from ethanol–water as colourless needles, m. p. 104—105° (Found: C, 64·45; H, 5·45; N, 6·85. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·85%). The amide (0·2 g.) in 2N-sodium hydroxide (2 ml.) was kept at room temperature for 1 hr.; acidification of the solution precipitated benzoylacetamide (0·1 g.) which separated from water as needles, m. p. and mixed m. p. 112—113°. Similarly, hydrogenation of 5-benzamido-3-phenyl*iso*oxazole gave N-β-*aminocinnamoylbenzamide* which crystallised from ethanol as needles, m. p. 179° (decomp.) (Found: C, 72·25; H, 5·3; N, 10·6. $C_{16}H_{14}O_2N_2$ requires C, 72·15; H, 5·3; N, 10·5%), hydrolysed to N-(*benzoylacetyl*)*benzamide*, needles (from ethanol), m. p. 168—169° (Found: C, 71·6; H, 4·95; N, 5·35. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·25%), and in addition 6-hydroxy-2 : 4-diphenylpyrimidine, m. p. and mixed m. p. 290°.

5-Formamido-3-phenyl*iso*oxazole hemihydrate gave N-β-*aminocinnamoylformamide* which separated from ethanol as laths, m. p. 155—156° (Found: C, 63·1; H, 5·15; N, 14·75. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·75%), hydrolysed to *N*-(benzoylacetyl)formamide, needles (from water), m. p. 114° (Found: C, 62·3; H, 4·4; N, 7·4. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·75; N, 7·35%); at the same time a second *substance* was isolated, and crystallised as needles (from ethanol), m. p. 144—145° (decomp.) (Found: C, 67·2; H, 4·55; N, 8·7. $C_9H_7O_2N$ requires C, 67·1; H, 4·35; N, 8·7%), and in addition 2-hydroxy-4-phenylpyrimidine, m. p. 268° (Found: C, 69·5; H, 4·5; N, 16·05. Calc. for $C_{10}H_8ON_2$: C, 69·75; H, 4·7; N, 16·25%). Seide (*Ber.*, 1925, **58**, 352) gives m. p. 267°.

Cylisation of β-*Aminocinnamoylacylamines* (VIII).—(i) *N*-β-Aminocinnamoylacetamide (40·8 mg.) was heated for a short time at the m. p.; a loss in weight (4·1 mg. Calc. for $1H_2O$: 3·7 mg.) occurred. Crystallisation of the product gave 6-hydroxy-2-methyl-4-phenylpyrimidine. (ii) The amine (0·6 g.) was boiled with water (60 ml.) for 2 hr.; a crystalline precipitate appeared after 1½ hr. The solution was evaporated to a small volume and the solid hydroxypyrimidine (0·5 g.) collected. (iii) A solution of the amine (0·05 g.) in ethanol (5 ml.) and water (10 ml.) was kept at 35°; the hydroxypyrimidine crystallised from the solution overnight. (iv) A solution of the amine (0·1 g.) in N-sodium hydroxide (4 ml.) was kept at room temperature for 10 min.; acidification of the solution precipitated the hydroxypyrimidine (0·07 g.). Similar series of reactions were performed with the benzamide and formamide derivatives, the latter compound proving the most labile.

Ethyl 5-*Amino*-3-*methyl*iso*oxazole*-4-*carboxylate* (II; R = Me).—A solution of ethyl 2-cyano-3-oxobutanoate (3·1 g.) in ethanol (50 ml.) containing hydroxylamine hydrochloride (1·4 g.) and pyridine (2 ml.) was warmed on a water-bath for 1 hr. The solution was evaporated to a small volume, and water (50 ml.) added, to precipitate the iso*oxazole* ester (2·1 g.) which recrystallised from water as colourless needles, m. p. 133—134° (Found: C, 49·65; H, 5·7; N, 17·0. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%). The ester (1 g.) was kept at room temperature with N-sodium hydroxide (5 ml.) for 30 min. and the solution then acidified, to give 5-*amino*-3-*methyl*iso*oxazole*-4-*carboxylic acid* (0·6 g.) which recrystallised from ethanol–water as colourless needles, m. p. 161—162° (decomp.) (Found: C, 42·2; H, 4·15; N, 19·1. $C_5H_6O_3N_2$ requires C, 42·25; H, 4·25; N, 19·7%); the acid gave a red colour with ferric chloride in ethanol. A solution of the acid (0·5 g.) in N-sodium hydroxide solution (5 ml.) was warmed on a water-bath for 10 min., then cooled, and the solid collected; 5-amino-3-methyl*iso*oxazole (0·25 g.) crystallised from water as needles, m. p. 85° undepressed on admixture with an authentic specimen of m. p. 84—85° (Burns, *loc. cit.*).

We thank Dr. E. Challen for the semimicro-analyses.

THE UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA.

[*Received, October 6th*, 1953.]

The Action of Sodium in Liquid Ammonia on Phaeanthine, OO′-Dimethylcurine, and OO′-Dimethylisochondrodendrine.

By D. A. A. KIDD and JAMES WALKER.

[Reprint Order No. 4757.]

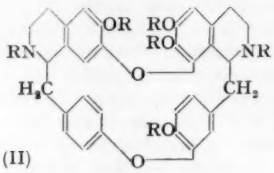
The sodium–liquid ammonia fission process has been applied to phaeanthine (II; R = Me), *OO′*-dimethylcurine (IV; R = Me), and *OO′*-dimethyl-*iso*chondrodendrine (V; R = Me), as typical representatives of three groups of bisbenzyl*iso*quinoline alkaloids, particular regard being paid to the homogeneity of the direction of cleavage of the diaryl ether linkages. In benzene–toluene solution fission of phaeanthine and of *OO′*-dimethylcurine gave only (−)-*O*-methylarmepavine (VIII) as non-phenolic product and (−)-*N*-methylcoclaurine (IX) as sole phenolic product. In dioxan solution, however, evidence of other modes of fission was obtained, but only the phenolic products of the alternative modes of cleavage have been isolated; that from phaeanthine has not been identified with certainty but it was neither corpaverine (XI) nor laudanidine (XII), while that from *OO′*-dimethylcurine was identified as laudanidine [(−)-laudanine] (XII). Cleavage of *OO′*-dimethyl*iso*chondrodendrine in dioxan solution gave (−)-armepavine (XVII) as the only product that could be characterised, but evidence for the formation of two others was obtained.

A synthesis of (±)-*N*-methylcoclaurine (IX) is described.

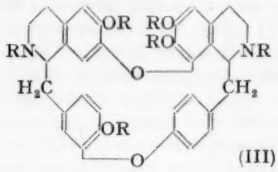
THE bisbenzyl*iso*quinoline (biscoclaurine) alkaloids are derived formally by linking together two 1-benzyl*iso*quinoline units by one, more often two, or even three, diaryl ether linkages, and Faltis has suggested (Faltis and Frauendorfer, *Ber.*, 1930, **63**, 808; Faltis, Holzinger, Ita, and Schwarz, *ibid.*, 1941, **74**, 79) that they may arise in the plant by enzymic dehydrogenation and condensation of coclaurine (I). Considering only those alkaloids with two diaryl ether linkages, four distinct groups are known: (II), which includes berbamine, phaeanthine, tetrandrine, *iso*tetrandrine, menisine, fangchinoline, and cepharanthine; (III), which includes oxyacanthine, repandine, aromoline, trilobamine, daphnandrine, epistephanine, and hypoepistephanine; (IV), which includes curine, bebeerine, tubocurarine (quaternary), chondrofoline, and chondrocurine; and (V), which includes *iso*chondrodendrine, cycleanine, protocuridine, and *neo*protocuridine. In addition to this structural isomerism, the alkaloids of these four groups vary with regard to the degree of *O*- or *N*-methylation (R = H or Me in II—V), and in configurations at the asymmetric centres; apart from the incidental circumstances that cepharanthine contains a methylenedioxy-group, and epistephanine and hypoepistephanine have each one dihydro*iso*quinoline nucleus, all are seen to be derivable theoretically from two molecules of the coclaurine type by similar means. Attack by the 7- and 4′-hydroxyl groups of one coclaurine-type molecule on the unsubstituted 8- and 3′-positions of another leads to type (II), and on the 3′- and 8-positions of the other respectively to type (IV); or the 7-hydroxyl group of one molecule may attack the 8-position of another, while the 3′-position of the first is attacked by the 4′-hydroxyl group of the second, leading to type (III); or the 4′-hydroxyl groups of two coclaurine type molecules may simultaneously attack the 8-positions of each other leading to type (V).

It has recently been shown that when certain bisbenzyl*iso*quinoline alkaloids are reduced with sodium (or potassium) in liquid ammonia in toluene or benzene solution, cleavage of the diaryl ether linkages occurs in such a way as to yield, apparently exclusively, products of the coclaurine type (I), thus reversing formally what may possibly be the biogenetic mode of synthesis. For the first time also the differentiation of alkaloids of type (II) from those of type (III) has been made possible. At the outset of the work described in the present communication, part of which has been the subject of a preliminary note (*Chem. and Ind.*, 1953, 243), this technique had been applied to *iso*tetrandrine (Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 226, 1035; Tomita, Inubushi, and Niwa, *ibid.*,

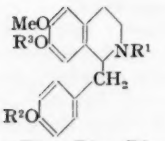
1952, **72**, 211), tetrandrine (Tomita, Fujita, and Murai, *ibid.*, 1951, **71**, 301; Fujita and Murai, *ibid.*, p. 1039) and berbamine (Inubushi, *ibid.*, 1952, **72**, 220) belonging to group (II), to *O*-methyloxyacanthine (Fujita, *ibid.*, 1952, **72**, 213, 217) belonging to group (III), and to cycleanine (Tomita, Fujita, and Murai, *ibid.*, 1951, **71**, 301; Fujita and Murai, *ibid.*, p. 1043) belonging to group (V); while, in the interval, it has also been applied to *O*-methylrepandine (Fujita and Saijoh, *ibid.*, 1952, **72**, 1232) and to dauricine (Inubushi and Niwa,



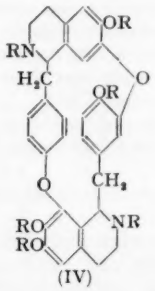
(II)



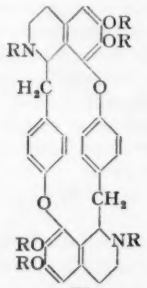
(III)



(I) $R^1 = R^2 = R^3 = H$
(VIII) $R^1 = R^2 = R^3 = Me$
(IX) $R^1 = Me$, $R^2 = R^3 = H$
(XVII) $R^1 = R^3 = Me$, $R^2 = H$



(IV)

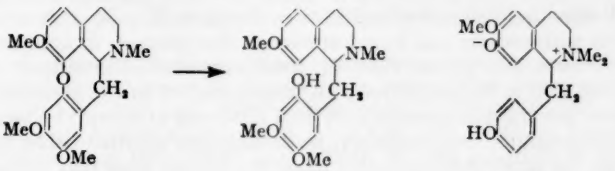


(V)

ibid., p. 762), which contains only one diaryl ether linkage. In every case only substances of the coclaurine type have been reported as the products of complete fission of the diaryl ether linkages. This apparent homogeneity of the fission process is surprising, as one would expect, on the basis of the sodium–liquid ammonia fission of model diaryl ethers (Sartoretto and Sowa, *J. Amer. Chem. Soc.*, 1937, **59**, 603; Kranzfelder, Verbanc, and Sowa, *ibid.*, p. 1488; Weber and Sowa, *ibid.*, 1938, **60**, 94), to obtain mixtures resulting from fission of the diaryl ether linkages at *either* side of the oxygen atoms to varying extents. The sodium–liquid ammonia cleavage of cularine (VI) to give (VII) as apparently sole product (Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55) is feasible when one notes that the reductions of 2-methoxy-, 2 : 3′-dimethoxy-, and 2 : 4′-dimethoxy-diphenyl ether give respectively 45, 24, and 1% of guaiacol (Sowa *et al.*, *locc. cit.*). In general, however, and particularly with unsymmetrical diaryl ethers with 2 : 2′-dimethoxy-substitution, one would expect detectable amounts of other products to be formed. We have therefore examined carefully the sodium–liquid ammonia fission products from phaeanthine (II; R = Me), *OO*′-dimethylcurine (IV; R = Me), and *OO*′-dimethyl*iso*chondrodendrine (cycleanine) (V; R = Me), as typical representatives of three distinct groups, with the object of finding out if, and to what extent, alternative modes of cleavage may occur. The starting materials were shown to be chromatographically homogeneous and paper chromatography was used in the examination of fission products.

In benzene–toluene solution the cleavage of phaeanthine (II; R = Me) went smoothly to completion and gave a syrupy non-phenolic product and a crystalline phenolic substance. The non-phenolic material was shown to be homogeneous by paper chromatography and, apart from the fact that it was not obtained crystalline in this instance, its properties agreed in detail with those recorded for (−)-*O*-methylarmepavine (VIII). Similarly, the phenolic product of fission was shown to be homogeneous, and although its physical constants (m. p. 176°, $[\alpha]_D^{23}$ −69·6°) were, apart from the sign rotation, markedly different from those (m. p. 137—138·5°, $[\alpha]_D^{16}$ +88·51°) recorded for the enantiomorph (Tomita, Fujita, and Murai, *J. Pharm. Soc. Japan*, 1951, **71**, 1035), it could only have been (−)-*N*-

methylcoclaurine (IX), since it gave a product identical with the non-phenolic fraction on treatment with diazomethane and afforded (−)-magnocurarine (X) on quaternisation. Incidentally, the isolation of (−)-*N*-methylcoclaurine (IX) and of (−)-*O*-methylarmepavine (VIII) from the cleavage of phaeanthine (II; R = Me) completes confirmation of the formulation of the latter alkaloid as the enantiomorph of tetrandrine (Kondo and Keimatsu, *Ber.*, 1935, **68**, 1503). It is also of interest to note that phaeanthine (II; R = Me) and (+)-magnocurarine (X) are found together in the bark of *Gyrocarpus americanus* Jacq. (McKenzie and Price, *Austral. J. Chem.*, 1953, **6**, 180), and it may well be, if the Faltis scheme of biogenesis is correct, that the plant makes both enantiomorphs of *N*-methylcoclaurine (IX) and converts the (−)-form into phaeanthine (II; R = Me) and quaternises the (+)-form to (+)-magnocurarine (X). The cleavage of *OO'*-dimethylcurine (IV;

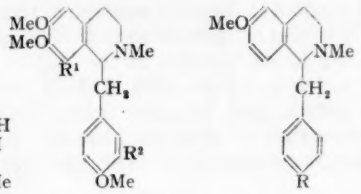


R = Me) in benzene–toluene proceeded rather less smoothly and the presence of some unchanged starting material was noted in the product. The products of fission, however, consisted of a single non-phenolic substance, (−)-*O*-methylarmepavine (VIII), and a single phenolic substance, (−)-*N*-methylcoclaurine (IX), identical with the fission products obtained from phaeanthine (II; R = Me) in the same circumstances. The isolation of these two lævorotatory fragments from *OO'*-dimethylcurine (IV; R = Me) also confirms the fact that both asymmetric centres in *dextro*bebeerine are dextrorotatory (King., *J.*, 1948, 265).

When cleavage was effected in dioxan solution, phaeanthine (II; R = Me) gave, as before, (−)-*O*-methylarmepavine (VIII), which was now obtained in a crystalline condition, but no other non-phenolic product was detected. The phenolic fraction yielded again (−)-*N* methylcoclaurine (IX), but, in addition, a small amount of a second phenolic component, m. p. 125—127°, was isolated. As it gave a strong Gibbs reaction (*J. Biol. Chem.*, 1927, **72**, 649) it was obviously not a demethylation product and it must have arisen by an alternative mode of fission from that giving (VIII) and (IX). The amount of material available was too small for extensive examination but it was shown to be distinct from corpaverine (XI) (Manske, *J. Amer. Chem. Soc.*, 1952, **74**, 2864), although the melting points were not far apart, and it was also shown not to contain laudanidine (XII). By exclusion it must have been the dihydric phenol (XIII), although no trace of the complementary non-phenolic fragment (XIV) was found; alternatively, it might conceivably have been produced by cleavage of only one of the two diaryl ether linkages but, in any event, no intermediate of such a type giving a positive Gibbs reaction could ultimately give rise to (VIII) and (IX).

When *OO'*-dimethylcurine (IV; R = Me) was similarly reduced in dioxan solution the reaction appeared to go to completion; the non-phenolic fraction again appeared to be homogeneous (VIII) and it was characterised as the methiodide. The phenolic fraction was, however, clearly a mixture and pure (−)-*N*-methylcoclaurine (IX) was isolated with some difficulty. In addition, a fraction was isolated having properties agreeing closely with those recorded for laudanidine [(−)-laudanine] (XII), and identity was confirmed by paper chromatography in comparison with (±)-laudanine (XII), and, after methylation with diazomethane, with (±)-laudanosine (XV). The phenolic fragment (XVI), complementary to (XII) from (IV; R = Me), was not isolated, and, although it would not have given a Gibbs reaction it could, in favourable circumstances, have been detected by paper chromatography. With both phaeanthine (II; R = Me) and *OO'*-dimethylcurine (IV; R = Me), therefore, sodium–liquid ammonia cleavage may, under appropriate condi-

tions, give products other than those (VIII) and (IX) of the coclaurine type; such a mode of fission is not detectable if reduction is carried out in benzene–toluene solution, and the extent to which it occurs is only small if cleavage takes place in dioxan solution.



(XI) $R^1 = OH$, $R^2 = H$
(XII) $R^1 = H$, $R^2 = OH$
(XIII) $R^1 = R^2 = OH$
(XV) $R^1 = H$, $R^2 = OMe$

(XIV) R = H
(XVI) R = OH

When *OO'*-dimethyl*iso*chondrodendrine (cycleanine) (V; R = Me) was reduced in dioxan solution with sodium and liquid ammonia, the product, in agreement with Fujita and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1043), consisted essentially of (−)-armepavine (XVII), agreeing well in its properties with those recorded in the literature. In addition however, two further substances must have been produced to account for two spots observed on paper chromatograms, but, curiously, no satisfactory positive Gibbs reaction was observed although the product of any other mode of cleavage than that giving (XVII) would have been unsubstituted in the *p*-position to a phenolic hydroxyl group. Predominantly, therefore, sodium–liquid ammonia cleavage of all three of these typical bisbenzyl*iso*quinoline alkaloids leads to substances of the coclaurine type, and fission in alternative directions occurs to a slight extent only.

As the properties of our (−)-*N*-methylcoclaurine (IX) were markedly different, apart from the sign of rotation, from those recorded for the enantiomorph, (±)-*N*-methylcoclaurine was synthesised, but numerous attempts to effect its resolution were unsuccessful. The (±)-substance was not distinguishable chromatographically from the optically active material from phaeanthine or from *OO'*-dimethylcurine, and the same applied to the derived methiodides [(±)- and (−)-magnocurarine iodide]. The synthesis followed conventional lines but several stages constitute improvements over previously known methods.

Experimental

Paper Chromatography.—Whatman's No. 1 paper was immersed in aqueous 0·2M-potassium dihydrogen phosphate, pressed between filter papers to remove excess of liquid, dried at 100°, and allowed to equilibrate against atmospheric moisture for several hours before use. Development was effected by the downward technique in sealed tanks, with, as routine solvent systems, the upper layers of the following mixtures, which gave the best results of a range examined: solvent A, amyl alcohol (110 c.c.), pyridine (110 c.c.), and water (sufficient to saturate, about 90 c.c.); solvent B, *n*-butanol (63 c.c.), acetic acid (10 c.c.), and water (27 c.c.). In some runs a second solvent front was observed but this did not interfere with the formation of spots which usually preceded it; it could be avoided by substituting the phosphate solution, used for impregnating the paper, for water in the above solvent mixtures, and R_F values were not noticeably affected by this substitution. For the detection of alkaloidal spots, the Dragendorff reagent (Munier and Macheboeuf, *Bull. Soc. Chim. biol.*, 1949, **31**, 1144) was used for non-phenolic substances; with phenolic alkaloids, however, the red spots obtained with this reagent were too transient, and the Folin–Denis reagent followed by alcoholic ammonia (Dalgliesh, *J.*, 1952, 3943) was more satisfactory. R_F values were usually reproducible within narrow limits but occasional variations occurred; comparisons between substances were always made directly by running samples, reference specimens, and mixtures of the two side by side.

Phaeanthine, *OO'*-dimethylcurine, and *OO'*-dimethyl*iso*chondrodendrine used in the following experiments were shown to be chromatographically homogeneous.

Reductive Cleavage of Phaeanthine (II; R = Me) *in Toluene–Benzene.*—A solution of phaeanthine (0·5 g.) in toluene (20 c.c.) and benzene (20 c.c.) was added dropwise to stirred liquid ammonia (500 c.c.) containing a small piece of sodium, and more sodium (total, 0·5 g.) was added whenever the blue colour faded until the reaction was at an end (blue colour relatively stable; time, 1½ hr.). After spontaneous evaporation of the ammonia, water was added, and the layers

were separated. The organic phase was washed with aqueous sodium hydroxide and water, then dried and evaporated, yielding a yellow syrup (Ph_1) (0·27 g.). The combined alkaline solutions were carbonated with solid carbon dioxide, and the phenolic product was obtained as a tan-coloured solid (Ph_2) (0·23 g.).

The readily-soluble non-phenolic syrup (Ph_1) did not crystallise and no seed was at the time available. It was, however, homogeneous as shown by paper chromatography since it gave single compact spots with both solvent systems A and B, and it had $[\alpha]_D^{23}$ −82·3° (*c*, 1·78 in $CHCl_3$). On treatment with methyl iodide (0·2 c.c.) in boiling methanol (10 c.c.) it afforded a crystalline methiodide, which separated from methanol in small cream-coloured prisms, m. p. 136—137°, sintering at 127—128° (Found: C, 51·8; H, 6·4; N, 2·9. Calc. for $C_{21}H_{28}O_3NI,H_2O$: C, 51·7; H, 6·2; N, 2·9%). Apart from the fact that it was not obtained crystalline in this instance, these properties are consistent with those of (−)-*O*-methylarmepavine (VIII), for which Tomita, Fujita, and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1035) record m. p. 62°, $[\alpha]_D^{16}$ −83·26° (methiodide, m. p. 135—136°), and Yunnussoff, Konowalowa, and Orechoff (*J. Gen. Chem., U.S.S.R.*, 1940, **10**, 641; *Chem. Zentr.*, 1941, I, 2530) record m. p. 64°, $[\alpha]_D$ −84·48° (methiodide, m. p. 135—136°).

The phenolic fraction (Ph_2) was also shown to be homogeneous by paper chromatography, and recrystallisation from benzene or toluene gave well-defined prisms of (−)-N-*methylcoclaurine* (IX), m. p. 176—177°, $[\alpha]_D^{23}$ −69·6° (*c*, 0·85 in $CHCl_3$) (Found: C, 72·4; H, 7·1; N, 4·4; OMe, 10·0. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1; N, 4·7; OMe, 10·4%). Tomita, Fujita, and Murai (*loc. cit.*) record m. p. 137—138·5°, $[\alpha]_D^{16}$ +88·51° (*c*, 0·14 in $CHCl_3$) for the hemihydrate (from methanol) of (+)-*N*-methylcoclaurine obtained by fission of *iso*tetrandrine, and Fujita and Murai (*ibid.*, p. 1039) record m. p. 138—139·5°, $[\alpha]_D^{16}$ +87·33° (*c*, 0·11 in $CHCl_3$) for the same base obtained from tetrandrine.

Reductive Cleavage of Phaeanthine in Dioxan.—Phaeanthine (1·5 g.), dissolved in anhydrous dioxan (35 c.c.), was reduced under conditions similar to those described above and the products were separated into a syrupy non-phenolic fraction (0·56 g.) and a phenolic fraction (0·9 g.). From the non-phenolic fraction *O*-methylarmepavine (Ph_1) was now obtained crystalline by slow evaporation of an ethereal solution, which afforded hard prisms, m. p. 60—61° (lit., m. p. 62—64°); all attempts at recrystallisation were, however, unsuccessful. The methiodide, prepared as before, was recrystallised twice from methanol, and both the pure substance and the mother-liquor residues were examined by paper chromatography; single spots were obtained in all cases, of R_F 0·52 in solvent A and R_F 0·64 in solvent B.

The phenolic product, obtained this time as a glass, was triturated with light petroleum, and the resulting solid was recrystallised twice from toluene, giving (−)-*N*-methylcoclaurine (Ph_2) (0·45 g.), m. p. 176—177°, $[\alpha]_D^{23}$ −69·2° (*c*, 0·98 in $CHCl_3$). The partly purified substance, the pure material, and the mother-liquor residues were examined by paper chromatography in solvent B. The impure solid gave two distinct spots of R_F 0·71 and 0·85; the pure substance (Ph_2) gave one spot of R_F 0·75, while the mother-liquor residues gave one spot of R_F 0·87. Evaporation of the mother-liquors gave a syrup which solidified under light petroleum, and recrystallisation from toluene gave a minute amount of a microcrystalline solid (Ph_3), m. p. 125—127°, giving a strong Gibbs reaction.

Methylation of (−)-N-*Methylcoclaurine* (Ph_2) *to* (−)-O-*Methylarmepavine* (Ph_1).—A solution of (−)-*N*-methylcoclaurine (Ph_2) (0·3 g.) in benzene (10 c.c.) and methanol (20 c.c.) was slowly added to ethereal diazomethane (from 5 g. of methylnitrosourea) during 1½ hr. After 1 hr. a further (equal) quantity of ethereal diazomethane was added, and the excess of diazomethane was allowed to evaporate. The solution was washed with aqueous sodium hydroxide and water, dried, and evaporated, yielding methylated Ph_2 as a yellow syrup (0·24 g.), $[\alpha]_D^{21}$ −77·7° (*c*, 1·61 in $CHCl_3$); this solidified spontaneously but the substance, m. p. 42—47°, could not be recrystallised. On comparison with substance Ph_1 by paper chromatography the two substances gave identical spots of R_F 0·75 in solvent A and 0·83 in solvent B. The methiodide from methylated Ph_2 formed yellowish prisms, m. p. 136—137° (sintering at 127—128°), and could not be distinguished from the methiodide of substance Ph_1 either by mixed m. p. or by infra-red spectrum (Nujol mull).

Attempted Identification of Substance Ph_3.—(*a*) Corpaverine, m. p. 140—141°, and substance Ph_3 were compared by paper chromatography and shown to be distinct, the former running somewhat faster than the latter in both solvents A and B; mixtures of the two gave linked spots. *X*-Ray powder photographs of the two substances were superficially similar in general pattern but showed significant differences in detail.

(*b*) A small quantity of substance Ph_3 was methylated with diazomethane in the usual way

and the product, a yellow syrup, was compared with (±)-laudanosine by paper chromatography. The latter ran rather more slowly than methylated Ph_3 in both solvents, and mixtures of the two substances gave elongated dumb-bell spots with both solvents, indicating non-identity.

Reductive Cleavage of OO′-*Dimethylcurine* (IV; R = Me) *in Toluene–Benzene.*—The curine used had been isolated by Dr. Harold King. It was methylated with diazomethane essentially as described by Späth, Leithe, and Ladeck (*Ber.*, 1928, **61**, 1698), and the product was chromatographed on alumina in benzene–light petroleum and eluted with benzene containing 1% of methanol. Evaporation of the various fractions gave amorphous (*X*-ray) material, and fractions of m. p. 116—121° were bulked for subsequent use.

OO′-Dimethylcurine (1 g.), dissolved in benzene (20 c.c.) and toluene (20 c.c.), was treated with sodium (approx. 1 g. required) in liquid ammonia as described above for phaeanthine, reaction being complete in about 2 hr. The product was separated, as before, into a non-phenolic syrup (0·59 g.) and a semi-solid phenolic fraction (0·34 g.).

The presence of unchanged *OO′*-dimethylcurine in the crude non-phenolic product was shown by paper chromatography, and the other component (Cu_1) and substance Ph_1 from phaeanthine, run side by side, had R_F values of 0·79 and 0·81 in solvent A and 0·88 and 0·90 in solvent B. The crude product was treated with methyl iodide (0·3 c.c.) in boiling methanol and one recrystallisation from methanol gave the methiodide of substance Cu_1 in the form of cream-coloured prisms, m. p. 137—138°, sintering at 123—125°, $[\alpha]_D^{23}$ −98·6° (*c*, 2·43 in $CHCl_3$) (Found: C, 51·5; H, 6·2; N, 3·4%). No depression of the m. p. was observed on admixture with the methiodide of substance Ph_1, and the two methiodides also gave identical infra-red spectra (Nujol mulls) and *X*-ray powder photographs.

The phenolic fraction was shown to be homogeneous by paper chromatography, and recrystallisation from benzene, toluene, or acetone gave substance Cu_2 in colourless lances or rectangular prisms, m. p. 173—175° (not depressed on admixture with substance Ph_2), $[\alpha]_D^{23}$ −67·0° (*c*, 0·28 in $CHCl_3$) (Found: C, 72·3; H, 6·8; N, 5·0%). The analytical data and physical properties, including infra-red spectra, of substances Cu_2 and Ph_2 showed them to be identical [(−)-*N*-methylcoclaurine]; in solvents A and B substance Cu_2 had R_F values of 0·73 and 0·77 respectively, while substance Ph_2 had an R_F value of 0·75 in both solvents.

Reductive Cleavage of OO′-*Dimethylcurine in Dioxan.*—A solution of *OO′*-dimethylcurine (1·5 g.) in anhydrous dioxan (30 c.c.) was gradually added to liquid ammonia and reduced with sodium under the conditions described above. Reaction took 2 hr. and the product, when partitioned in the usual way, gave a non-phenolic syrup (0·25 g.) and a phenolic glass (1·03 g.). The former was converted into the methiodide in the usual way and recrystallisation from methanol gave substance Cu_1 methiodide, m. p. 138—139°.

The phenolic material was shown by paper chromatography to be inhomogeneous, and it was recrystallised three times from toluene, giving substance Cu_2, m. p. 166°, which was still not quite pure. Evaporation of the mother-liquors from the first two recrystallisations gave gummy residues, in each case giving a positive Gibbs reaction, whereas the residue from the mother-liquors of the third recrystallisation and substance Cu_2 itself gave no reaction. The combined residues from the first two mother-liquors were dissolved in benzene containing 2% of methanol and chromatographed on a column of alumina (12 g.) made up in the same solvent. The first three fractions to be eluted were evaporated and the residues were taken up together in a little methanol from which large colourless prisms (substance Cu_3) (40 mg.) crystallised overnight; these had m. p. 182—183° (micro) (depressed to 163—164° on admixture with pure substance Cu_2, m. p. 173—175°), $[\alpha]_D^{20}$ −99·2° (*c*, 5·06 in $CHCl_3$), and gave a strong Gibbs reaction.

Methylation of (−)-N-*Methylcoclaurine* (Cu_2) *to* (−)-O-*Methylarmepavine* (Cu_1).—A solution of substance Cu_2 (0·1 g.) in methanol (20 c.c.) and benzene (10 c.c.) was methylated with diazomethane (from 3 g. of methylnitrosourea) in the manner described for substance Ph_2, and the product was converted in the usual way into the methiodide, m. p. 138—139°, shown by mixed m. p. and infra-red spectrum (Nujol mull) to be identical with the methiodide of substance Cu_1.

Identification of Substance Cu_3 *as Laudanidine* (XII).—The properties of substance Cu_3 (m. p. 182—183°, $[\alpha]_D^{20}$ −99·2°) were in close agreement with those of laudanidine [(−)-laudanine], for which Späth and Bernhauer (*Ber.*, 1925, **58**, 200) record m. p. 184—185°, $[\alpha]_D^{18}$ −100·6°. The colour reactions tallied with those described for laudanine; with concentrated sulphuric acid substance Cu_3 gave a faint pink colour darkening rapidly to purple-red on heating (cf. Hesse, *Annalen, Suppl.*, 1872, **8**, 273), and a methanolic solution was rendered pale green by a drop of aqueous ferric chloride (cf. Hesse, *Annalen*, 1870, **153**, 54; 1894, **286**, 208). On comparison by paper chromatography of substance Cu_3 with (±)-laudanine, obtained by demethylation of (±)-laudanosine with hydrochloric acid (Späth and Burger, *Monatsh.*, 1926, **47**, 733), both sub-

stances had identical R_F values in both solvent systems (0·70 in A, and 0·57 in B), and mixtures of the two afforded single spots with both solvents.

Substance Cu_3 (9·2 mg.) was treated in methanol (2 c.c.) with diazomethane (from 1·5 g. of methylnitrosourea) in ether (15 c.c.). After 16 hr. the excess of diazomethane was destroyed with acetic acid, and the mixture was basified with ammonia, the ethereal layer being washed with aqueous sodium hydroxide, then with water, then dried, and evaporated. The residue (9 mg.) was crystalline, m. p. 76—77°; for optically active laudanosine, Pictet and Athanasescu (*Ber.*, 1900, **33**, 2346) record m. p. 89°. When run in solvents A and B the substance had R_F values of 0·72 and 0·66 respectively, while (±)-laudanosine had R_F values of 0·73 and 0·64; mixtures of methylated Cu_3 and (±)-laudanosine gave single spots of R_F 0·73 and 0·64 in solvents A and B respectively.

Conversion of (−)-N-*Methylcoclaurine* (IX) *into* (−)-*Magnocurarine* (X).—(−)-*N*-Methylcoclaurine (0·7 g.), derived from phaeanthine, was refluxed in methanol (30 c.c.) with methyl iodide (1 c.c.) for 1 hr. Crystals (0·83 g.) separated during concentration of the solution, and recrystallisation from methanol afforded (−)-N-*methylcoclaurine methiodide* [(−)-*magnocurarine iodide*] in fine cream-coloured leaflets or flat prisms, m. p. 194—197°, sintering at 149° (Found: C, 49·6; H, 5·8; N, 2·9. $C_{19}H_{24}O_3NI,H_2O$ requires C, 49·7; H, 5·7; N, 3·1%).

The major part of the methiodide was converted into the methochloride (cf. Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 5231) by refluxing for 1 hr. with methanol (50 c.c.) of which part (30 c.c.) had been saturated with hydrogen chloride. Evaporation to dryness left a brown syrup which was taken up in a little methanol and brought to pH 7—8 with methanolic 0·5N-potassium hydroxide. A portion of the neutralised solution was diluted with water, and the methanol was evaporated; saturated aqueous sodium picrate was added and the precipitated picrate crystallised from acetone in yellow needles, m. p. 172—173°: Tomita, Inubushi, and Yamagata (*J. Pharm. Soc. Japan*, 1951, **71**, 1069) record m. p. 169—172°, and Tomita and Nakano (*ibid.*, 1952, **72**, 197) record m. p. 177—178° for (−)-magnocurarine picrate. The bulk of the neutralised methochloride solution deposited crystals of the phenol-betaine when set aside at pH 8; the colourless prisms which separated on recrystallisation from water containing a little methanol had m. p. 198—200°, $[\alpha]_D^{23}$ −89·6° (*c*, 1·2 in H_2O): Tomita, Inubushi, and Yamagata (*loc. cit.*) record m. p. 200°, $[\alpha]_D^{29}$ −91° (in H_2O) for (−)-magnocurarine, and McKenzie and Price (*loc. cit.*) record m. p. 198—199°, $[\alpha]_D^{22}$ +106° (in H_2O) for the enantiomorph.

Reductive Cleavage of OO'-*Dimethyliso*chondrodendrine (V; R = Me) *in Dioxan.*—(*a*) Powdered stems (1700 g.) of *Chondrodendron candicans* were extracted with 1% tartaric acid as described by King (*J.*, 1940, 737) and the crude chloroform-soluble bases (46 g.) were crystallised from methanol. *iso*Chondrodendrine was isolated from the resulting mixture as the sulphate, m. p. 305—309° (decomp.) $[\alpha]_D^{19}$ +107° (*c*, 0·58 in H_2O; on material dried *in vacuo* at room temperature). The homogeneity of the specimen was demonstrated by paper chromatography on phosphate-treated paper in solvent A, which is capable of effecting separation of *iso*chondrodendrine and bebeerine, the major alkaloids found in this species.

(*b*) A suspension of *iso*chondrodendrine (1·5 g.) in benzene (70 c.c.) and methanol (25 c.c.) was stirred during the addition during 2 hr. of a benzene solution (50 c.c.) of diazomethane (from 10 g. of methylnitrosourea). The mixture, which rapidly cleared, was stirred for a further ½ hr. and kept overnight before destruction of excess of diazomethane with acetic acid. Evaporation of the washed organic phase gave a crystalline residue (1·2 g.), from which pure *OO'*-dimethyl*iso*-chondrodendrine was obtained by recrystallisation from acetone as clusters of long, flat prisms, m. p. 273—275°, $[\alpha]_D^{19}$ −30·3° (*c*, 2·6 in EtOH); the substance gave single spots in both solvent systems. Faltis and Neumann (*Monatsh.*, 1921, **42**, 311) record m. p. 256—257°, $[\alpha]_D^{19}$ −36·8° (in EtOH), and Kondo, Tomita, and Uyeo (*Ber.*, 1937, **70**, 1890) record m. p. 272—273°, $[\alpha]_D^{31}$ −28·7°.

(*c*) *OO'*-Dimethyl*iso*chondrodendrine (0·5 g.) in dioxan (25 c.c.) was reduced with sodium (0·6 g.) in liquid ammonia (500 c.c.) as described above in the case of phaeanthine. The product was partitioned in the usual way, giving a syrupy non-phenolic fraction (0·1 g.) and a solid phenolic fraction (0·4 g.). The latter was taken up in warm ethanol (10 c.c.) and treated with oxalic acid (0·5 g.) in ethanol. The crystalline hydrogen oxalate (0·45 g.; m. p. 210—211°) which rapidly separated was recrystallised from ethanol giving colourless needles, m. p. 211—212°. Basification of the purified oxalate afforded (−)-armepavine (0·34 g.), which separated from a small volume of acetone–ether (5 : 1) as a crust of small needles, m. p. 149—150°, $[\alpha]_D^{21}$ −105° (*c*, 1·25 in $CHCl_3$). Fujita and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 1043) record m. p. 145—146°, $[\alpha]_D^{12}$ −109·1° (in $CHCl_3$) (oxalate, m. p. 211—212°), and Konowalowa, Yunussoff, and Orechoff (*Ber.*, 1935, **68**, 2158) record m. p. 148—149°, $[\alpha]_D$ −118·7° (oxalate, m. p. 211—212°).

The oxalate mother-liquors were basified and the liberated base (50 mg.) was isolated by extraction with chloroform. This crude residue, which gave no typical reaction with Gibbs's reagent, was compared with pure (−)-armepavine by paper chromatography; in solvent A, the latter gave a single compact spot of R_F 0·69, whereas the mother-liquor residues showed a corresponding spot of R_F 0·68 and two additional spots of R_F 0·57 and 0·76 respectively; in solvent B a similar result was obtained, the observed R_F values being 0·65 for armepavine, and 0·52, 0·63, and 0·74 for the mother-liquor residues.

The original crude non-phenolic fraction was dissolved in acetone and set aside for a week at 2°; no *OO'*-dimethyl*iso*chondrodendrine had separated at the end of this period, and none could be detected by paper chromatography. Chromatography on a column of alumina failed to yield any crystalline material.

7-Benzyloxy-1-4'-benzyloxybenzyl-3 : 4-dihydro-6-methoxyisoquinoline Hydrochloride.—The undernoted stages in this synthesis constitute improvements on previously described methods.

(*a*) A suspension of 4-nitrobenzyl cyanide (Pschorr, Wolfes, and Buckow, *Ber.*, 1900, **33**, 162) (100 g.) in a mixutre of ethyl acetate (450 c.c.) and ethanol (150 c.c.) was hydrogenated over 2% palladised strontium carbonate (1 g.) at an initial pressure of 10 atm. and room temperature until the theoretical amount of hydrogen was absorbed. Two such reaction mixtures were bulked, filtered, and taken to dryness. The residue was treated in chloroform (500 c.c.) with 5N-hydrochloric acid (350 c.c.). The precipitated hydrochloride was collected and the free base was liberated and taken up in ether, yielding, on evaporation, 4-aminobenzyl cyanide (133 g., 85%).

(*b*) 4-Hydroxybenzyl cyanide (77 g.), prepared from the amino-compound by the method of Koessler and Hanke (*J. Biol. Chem.*, 1919, **39**, 585), dissolved in the minimum amount of ethanol, was added to ethanolic potassium hydroxide (38·5 g. in 385 c.c.), and benzyl chloride (84 g.) was run in. After refluxing for 3 hr. the mixture was cooled, and the crystalline solid was collected and washed with ethanol. The solid was partitioned between ether and water, the organic phase was washed with 2N-sodium hydroxide and water, and the ether was evaporated; 4-benzyloxybenzyl cyanide, m. p. 68—70°, was thus obtained; Tomita, Nakaguchi, and Takagi (*J. Pharm. Soc. Japan*, 1951, **71**, 1046) record m. p. 68·5—69°. A further small quantity was isolated from the ethanolic mother-liquors, and, after recrystallisation from methanol, had m. p. 64—65° (total yield, 115·3 g.; 90%).

(*c*) The preceding nitrile (115·3 g.) was refluxed with potassium hydroxide (40 g.) in a mixture of water (800 c.c.) and ethanol (240 c.c.) for 5 hr. A further amount of aqueous potassium hydroxide (40 g. in 800 c.c.) was added and refluxing was continued for a further 8 hr. to complete the hydrolysis. When cold, the mixture was extracted with ether, and the aqueous phase was acidified, precipitating 4-benzyloxyphenylacetic acid (125 g., 99%), m. p. 120—122°; Mozingo and Folkers ("Chemistry of Penicillin," Oxford Univ. Press, 1949, p. 535) record m. p. 122°.

(*d*) The preceding acid (25 g.) was heated at 65—70° with thionyl chloride (5 c.c.) in ligroin (40 c.c.) until reaction ceased, leaving a clear solution. On cooling in ice, the acid chloride crystallised in quantitative yield, and was washed well with ligroin and dried *in vacuo*.

(*e*) A solution of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine hydrochloride (7 g.), prepared by Finkelstein's method (*J. Amer. Chem. Soc.*, 1951, **73**, 550), in chloroform (100 c.c.) was stirred with ice-cooling during the addition of triethylamine (4 c.c.) in chloroform (50 c.c.). After 30 min., a further similar quantity of triethylamine in chloroform and a solution of 4-benzyloxyphenylacetyl chloride (6·2 g.) in chloroform were added in portions alternately with continued stirring and cooling. An hour after addition was complete, water was added and the chloroform layer was separated and washed; evaporation then gave pure *N*-2'-(4-benzyloxy-3-methoxyphenyl)ethyl-4-benzyloxyphenylacetamide (10·9 g., 95%), m. p. 114—116°; Tomita, Nakaguchi, and Takagi (*loc. cit.*) record m. p. 115—117°.

(*f*) Phosphoryl chloride (26·7 c.c.) was added to a solution of the above amide (18·3 g.) in chloroform (43 c.c.), and the mixture was refluxed for 3½ hr. On dilution with several volumes of light petroleum and storage at 2° for 16 hr., a solid was obtained; this was well washed with light petroleum and dissolved in methanol (charcoal); addition of ether to the filtrate precipitated the hydrochloride of the required dihydro*iso*quinoline; the crystals (14·8 g., 86%), which separated, were sufficiently pure [m. p. 196—198° (decomp.)] for the next stage. Recrystallisation from alcohol raised the m. p. to 198—199° (decomp.); Tomita *et al.* (*loc. cit.*) record m. p. 197° (decomp.).

7-Benzyloxy-1-4'-benzyloxybenzyl-3 : 4-dihydro-6-methoxyisoquinoline Methiodide.—The above hydrochloride (10 g.) was dissolved in boiling ethanol (130 c.c.) and maintained at 65—70° while air was displaced with a stream of nitrogen. After 30 min., a solution of sodium ethoxide (from

0·5 g. of sodium) in ethanol (20 c.c.) was added, followed in a few minutes by methyl iodide (15 c.c.). Gentle boiling under nitrogen was continued for 5½ hr. The product, which crystallised from the cooled solution, was thoroughly ground with water, collected, washed with water, and dried (yield, 11·7 g., 96%; m. p. 188—190°). Recrystallisation from methanol–ether, or acetone–ether, gave light yellow platelets of the *methiodide*, m. p. 191—193° (Found: C, 63·7; H, 5·4; N, 2·0. $C_{32}H_{32}O_3NI$ requires C, 63·6; H, 5·3; N, 2·3%).

(±)-N-*Methylcoclaurine* (IX).—(*a*) The above methiodide (1·83 g.) was hydrogenated over Raney nickel in ethanol (500 c.c.) containing diethylamine (2·5 c.c.) for 3 hr. at 160° and an initial pressure of 60 atm. (cf. Barltrop and Taylor, *J.*, 1951, 108). Evaporation of the filtered solution gave a yellow solid residue (1·13 g.), which was extracted with successive portions of boiling toluene. On concentration to small bulk the toluene extracts gave a cream-coloured solid (0·2 g.; m. p. 152—156°), and a further crop (0·24 g.; m. p. 160—162°) was obtained from the mother-liquors. Recrystallisation from toluene, or from a small volume of acetone, gave small colourless prisms of (±)-*N*-methylcoclaurine, m. p. 161—162° (Found: C, 70·4; H, 7·5; N, 4·7. Calc. for $C_{18}H_{21}O_3N,\frac{1}{2}H_2O$: C, 70·1; H, 7·2; N, 4·5%); Tomita and Kusuda (*J. Pharm. Soc. Japan*, 1952, **72**, 280) record m. p. 161—162° for material prepared by *N*-methylation of natural (±)-coclaurine.

The synthetic (±)-material was indistinguishable by paper chromatography in both solvents A and B from (−)-*N*-methylcoclaurine obtained (above) by degradation of phaeanthine.

(*b*) The following procedure, though rather more tedious, gave a much better yield. The methiodide (5·9 g.) was converted into the methochloride with methanolic hydrogen chloride (cf. Phillips and Baltzly, *loc. cit.*). The crude methochloride (4·2 g.) was debenzylated by slow distillation at atmospheric pressure of its solution in 20% hydrochloric acid (175 c.c.) until no more benzyl chloride distilled over; the remaining solvent was then removed *in vacuo*. The residue was next reduced by being stirred for 3 hr. under reflux with zinc powder (7 g.) in boiling 30% acetic acid (50 c.c.) (cf. Schöpf, Jäckh, and Perrey, *Annalen*, 1932, **497**, 59). The cooled solution was filtered and the zinc was washed with 30% acetic acid. The acidic filtrates were basified with ammonia, and the product was recovered in ether, a further quantity being obtained by a subsequent extraction with chloroform. Recrystallisation from acetone then gave (±)-*N*-methylcoclaurine (2·1 g., 72%), m. p. 161—163°.

Unsuccessful attempts were made to resolve the (±)-substance using camphorsulphonic acid, α-bromocamphorsulphonic acid, camphoric acid, tartaric acid, dibenzoyltartaric acid, quinic acid, menthoxyacetyl chloride, and oleanolic acid.

(±)-N-*Methylcoclaurine Methiodide* [(±)-*Magnocurarine Iodide*].—(±)-*N*-Methylcoclaurine (0·3 g.) was treated with methyl iodide (0·5 c.c.) in boiling methanol (20 c.c.) for 1½ hr. Recrystallisation of the residue, left on evaporation, from a small volume of methanol gave the (±)-*methiodide* in the form of heavy cream-coloured prisms (0·28 g.), m. p. 155—156° (decomp.) (Found: C, 49·8; H, 5·8; N, 2·9. $C_{19}H_{24}O_3NI,H_2O$ requires C, 49·7; H, 5·7; N, 3·1%). The infra-red spectrum of the (±)-methiodide and that of the (−)-form showed very close correspondence but not complete identity (Nujol mulls), as could be expected. When compared by paper chromatography under standard conditions, the (±)- and (−)-methiodides had identical R_F values (0·72 in solvent A, and 0·48 in solvent B), and mixtures of the two gave single spots with both solvents.

The authors are indebted to Dr. J. R. Price for a generous gift of phaeanthine and to Dr. R. H. F. Manske for a specimen of corpaverine; they also thank Mrs. O. Kennard for providing *X*-ray powder photographs and Mr. R. J. Clark for technical assistance.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7.

[*Received, October 28th*, 1953.]

The Preparation of 4- *and* 5-n-*Alkoxy*-1-*naphthoic and* 6- *and* 7-n-*Alkoxy*-2-*naphthoic Acids.*

By G. W. Gray and Brynmor Jones.

[Reprint Order No. 4762.]

Each of the series of 4-*n*-alkoxy-1- and 6-*n*-alkoxy-2-naphthoic acids has been prepared by two methods which are compared. A new method of synthesising 5-hydroxy-1-naphthoic acid is compared with recorded methods. The same route has been used to prepare 7-hydroxy-2-naphthoic acid. Several *n*-alkyl ethers of these hydroxy-acids are described.

The preparation of certain alkoxynaphthoic acids was undertaken to obtain information about the effect of molecular shape on the mesomorphic behaviour of alkoxyarenecarboxylic acids. The simpler *p*-*n*-alkoxybenzoic acids have already been shown to exhibit mesomorphism (*J.*, 1929, 2660; 1935, 1874; 1939, 420; 1953, 4179), and preliminary reports of the mesomorphic behaviour of the 6-*n*-alkoxy-2-naphthoic acids and their 5-halogeno-derivatives have been made (Gray and Brynmor Jones, *Nature*, 1951, **167**, 83; 1952, **170**, 451). The preparation of four types of alkoxynaphthoic acid is now described.

4-*n*-Alkoxy-1-naphthoic acids could not be prepared by alkylation of 4-hydroxy-1-naphthoic acid, first reported by Heller (*Ber.*, 1912, **45**, 675). This acid is decarboxylated very easily, and Cavill and Tetaz (*J.*, 1952, 3634) report that it is difficult to obtain free from quinones. The *n*-alkoxy-acids were therefore prepared individually from the appropriate 1-*n*-alkoxynaphthalene, either by conversion into 1-*n*-alkoxy-4-bromonaphthalene and carboxylation of the Grignard compound, or by hydrolysis of 4-*n*-alkoxy-1-naphthonitrile prepared by Friedel and Crafts's reaction. The average over-all yield from the 1-*n*-alkoxynaphthalene was better by the second method (75%) than by the first (60%).

5-Hydroxy-1-naphthoic acid was first prepared (Royle and Schedler, *J.*, 1923, 1641) from the commercially available 5-aminonaphthalene-1-sulphonic acid. Their procedure, involving the intermediates, 5-cyano- and 5-carboxy-naphthalene-1-sulphonic acid, is however tedious. Cason (*J. Amer. Chem. Soc.*, 1941, **63**, 830) converted 5-amino-naphthalene-1-sulphonic acid into 5-amino-1-naphthonitrile, and claims that this may be hydrolysed to the hydroxy-acid by 10% sulphuric acid, in a sealed tube at 220° ± 5° during 4 hr. However, this hydrolysis could not be repeated. Temperatures above 225° gave mainly 1-naphthol; at 200—225° the product was a mixture which could not be purified, and between 180° and 200° only very slight hydrolysis to 5-amino-1-naphthoic acid occurred. As an alternative route, 5-amino-1-naphthonitrile was converted into 5-hydroxy-1-naphthonitrile, and this, by hydrolysis, into 5-hydroxy-1-naphthoic acid. This method is reliable, can be operated on any scale, and, although it involves one more stage than Cason's, gives a better yield. Alkylation of the hydroxy-acid gave the alkyl ethers.

6-Methoxy-2-naphthoic acid was prepared by two methods which differ little in overall yield or convenience: carboxylation of the Grignard compound from 2-bromo-6-methoxynaphthalene, and oxidation of 2-acetyl-6-methoxynaphthalene with sodium hypobromite. The methyl ether was readily demethylated to give 6-hydroxy-2-naphthoic acid.

7-Hydroxy-2-naphthoic acid was prepared by the procedure adopted for 5-hydroxy-1-naphthoic acid. 7-Aminonaphthalene-2-sulphonic acid was converted into 7-amino-2-naphthonitrile by distillation with potassium cyanide. Diazotisation yielded 7-hydroxy-2-naphthonitrile, and this, on hydrolysis, gave 7-hydroxy-2-naphthoic acid, from which the ethers were prepared.

In all cases except the last, thirteen normal ethers were prepared (methyl—decyl, dodecyl, hexadecyl, and octadecyl). The *n*-alkyl halides, which were not commercially available, were prepared from the normal alcohol, by the action of 48% hydrobromic acid and concentrated sulphuric acid (*Org. Synth.*, 1941, Coll. Vol. I, p. 29).

Experimental

M. p.s are corrected for exposed stem.

1-n-*Alkoxynaphthalenes.*—1-Naphthol was alkylated in boiling alcohol (8 hr.) by sodium ethoxide and the *n*-alkyl bromide or iodide. After distillation under reduced pressure, the ethers were obtained colourless in 65—75% yield (see Table).

1-n-*Alkoxynaphthalenes.*

Alkyl	M. p.	B. p.	Alkyl	M. p.	B. p.
Methyl	—	134°/13 mm.	Octyl	—	189°/5 mm.
Ethyl	5°	152°/17 mm.	Nonyl	—	185°/4 mm.
Propyl	—	143°/3 mm.	Decyl	—	212°/4 mm.
Butyl	19·5	160°/4 mm.	Dodecyl	—	227°/3 mm.
Pentyl	29·5	173°/6 mm.	Hexadecyl	31°	258°/1 mm.
Hexyl	−3	166°/4 mm.	Octadecyl	50·5°	236°/10^{-3} mm.
Heptyl	—	171°/5 mm.			

1-n-*Alkoxy*-4-*bromonaphthalenes.*—The 1-*n*-alkoxynaphthalenes were brominated by Militzer's method (*J. Amer. Chem. Soc.*, 1938, **60**, 256)—iodine monobromide in chloroform at 10—20°. After removal of the chloroform, the bromo-ethers were distilled under reduced pressure, being obtained colourless in 65—75% yields (see Table).

1-*Alkoxy*-4-*bromonaphthalenes.*

			Found (%)			Required (%)	
Alkyl	M. p.	B. p.	C	H	Formula	C	H
Methyl	—	159°/4 mm.	55·6	3·7	$C_{11}H_9OBr$	55·7	3·8
Ethyl	48·5°	158°/3 mm.	57·6	4·6	$C_{12}H_{11}OBr$	57·4	4·4
Propyl	31	188°/8 mm.	58·6	5·0	$C_{13}H_{13}OBr$	58·9	5·0
Butyl	25	199°/5 mm.	60·3	5·5	$C_{14}H_{15}OBr$	60·2	5·4
Pentyl	47·5	181°/3 mm.	61·5	5·7	$C_{15}H_{17}OBr$	61·5	5·8
Hexyl	45	206°/5 mm.	63·1	6·3	$C_{16}H_{19}OBr$	62·6	6·2

4-n-*Alkoxy*-1-*naphthonitriles.*—Cyanogen bromide (*Org. Synth.*, 1931, **11**, 30) was not dried by shaking it, when molten, with calcium chloride. When it was distilled slowly from the reaction mixture, the distillate contained little moisture. A known weight of the distillate, dissolved in carbon disulphide, was dried (Na_2SO_4) and used as a standard solution. With 1-*n*-alkoxynaphthalenes in carbon disulphide containing aluminium trichloride it gave the nitriles (Karrer, Zebmann, and Zeller, *Helv. Chim. Acta*, 1920, **3**, 267). The carbon disulphide extract was washed with aqueous sodium hydroxide to remove 4-hydroxy-1-naphthonitrile (1—2%), and dried (Na_2SO_4). Removal of the solvent gave solid residues which, on crystallisation from absolute ethyl alcohol, gave the alkoxy-nitriles (see Table) as colourless needles or prisms, in 80% yield.

4-*Alkoxy*-1-*naphthonitriles.*

		Found (%)				Required (%)		
Alkyl	M. p.	C	H	N	Formula	C	H	N
Ethyl	88°	79·2	5·6	7·0	$C_{13}H_{11}ON$	79·2	5·6	7·1
Penlyl	60	80·1	7·1	5·9	$C_{16}H_{17}ON$	80·3	7·1	5·9
Hexyl	62	80·5	7·4	5·4	$C_{17}H_{19}ON$	80·6	7·5	5·5
Heptyl	54	80·7	7·6	5·2	$C_{18}H_{21}ON$	80·9	7·8	5·2
Octyl	61	81·2	8·0	5·0	$C_{19}H_{23}ON$	81·1	8·2	5·0
Nonyl	53	81·4	8·6	4·6	$C_{20}H_{25}ON$	81·4	8·5	4·8
Decyl	64	81·5	8·7	4·3	$C_{21}H_{27}ON$	81·5	8·7	4·5
Dodecyl	67	82·0	9·2	4·0	$C_{23}H_{31}ON$	81·9	9·2	4·2
Hexadecyl	69	82·3	9·9	3·5	$C_{27}H_{39}ON$	82·4	9·9	3·6
Octadecyl	71	82·7	10·3	3·3	$C_{29}H_{43}ON$	82·7	10·2	3·3

Unsuccessful attempts were made to dealkylate these nitriles by refluxing them with 48% hydrobromic acid, with aluminium trichloride in carbon disulphide, and with acetic acid saturated with hydrogen bromide.

4-Hydroxy-1-naphthonitrile was very difficult to purify, and the best sample, obtained by crystallisation from 90% ethyl alcohol with heavy loss, had m. p. 172—174°. Its nitrogen content was low, and the acid formed on hydrolysis was impure (m. p. 174—175°; Heller, *loc. cit.*, gives m. p. 183—184°).

4-n-*Alkoxy*-1-*naphthoic Acids.*—(a) *From the bromo-compounds.* Magnesium turnings

(2·45 g., 0·1 g.-atom) and a solution of the 1-*n*-alkoxy-4-bromonaphthalene (2 g.) in ether (25 ml.) were refluxed for about 5 min. Appearance of turbidity indicated the start of the reaction. If this did not occur, small crystals of iodine were added, until, on the disappearance of the colour, a turbidity was visible. The remainder of the bromo-compound (total of 0·1 mole), in ether (75 ml.), was added dropwise in 30 min. to the stirred mixture, and refluxing continued for 10 hr. The resulting solution was added to ether which had been saturated with solid carbon dioxide. When the excess of carbon dioxide had evaporated, the addition compound was decomposed by stirring it with 17% hydrochloric acid (50 ml.). After the ether had been removed, the brown acid was collected and washed free from magnesium chloride. The crude acid was dissolved in boiling N-sodium hydroxide and filtered from insoluble material, and the pale orange filtrate was acidified. The acids were thus obtained in 80—85% yield as colourless solids which were almost pure after one crystallisation from glacial acetic acid.

(b) *From the nitriles.* The 4-*n*-alkoxy-1-naphthonitrile (0·1 mole) was refluxed with a solution (250 ml.) prepared by saturating methyl alcohol at 50° with potassium hydroxide. Evolution of ammonia ceased after 15—25 hours' boiling. The diluted mixture was acidified, and the precipitate of the naphthoic acid redissolved in boiling N-sodium hydroxide. The hot solution was filtered and acidified, to give quantitative yields of the colourless acids. These were almost pure after one crystallisation from glacial acetic acid (yields 95—97%).

In both cases, the 4-n-*alkoxy*-1-*naphthoic acids* were crystallised from glacial acetic acid until the m. p.s were constant (see Table).

4-Alkoxy-1-naphthoic acids.

		Found (%)			Required (%)	
Alkyl	M. p.	C	H	Formula	C	H
Methyl	248°	71·2	5·2	$C_{13}H_{10}O_3$	71·3	4·9
Ethyl	220	72·1	5·6	$C_{13}H_{12}O_3$	72·2	5·6
Propyl	203	73·1	6·1	$C_{14}H_{14}O_3$	73·1	6·1
Butyl	213·5	73·7	6·3	$C_{15}H_{16}O_3$	73·8	6·5
Pentyl	207	74·4	7·0	$C_{16}H_{18}O_3$	74·4	7·0
Hexyl	212	74·9	7·5	$C_{17}H_{20}O_3$	75·0	7·4
Heptyl	189	75·3	7·6	$C_{18}H_{22}O_3$	75·5	7·7
Octyl	183·5	75·9	8·1	$C_{19}H_{24}O_3$	76·0	8·0
Nonyl	161	76·3	8·2	$C_{20}H_{26}O_3$	76·4	8·3
Decyl	174·5	77·0	8·6	$C_{21}H_{28}O_3$	76·8	8·5
Dodecyl	147·5	77·5	9·0	$C_{23}H_{32}O_3$	77·5	9·0
Hexadecyl	136	78·4	9·6	$C_{27}H_{40}O_3$	78·6	9·7
Octadecyl	137·5	79·4	9·9	$C_{29}H_{44}O_3$	79·1	10·0

5-Amino-1-naphthonitrile.—Sodium 5-aminonaphthalene-1-sulphonate (70 g.) and potassium cyanide (140 g.) were ground together and dry-distilled in an all-glass retort, from a salt-bath at 500—600°. The red-brown distillate solidified and was dissolved in boiling 0·3N-hydrochloric acid (1·3 l.). The solution, cooled to 30°, was filtered to remove some tar; the filtrate was neutralised with concentrated aqueous ammonia, and the orange-brown precipitate of 5-amino-1-naphthonitrile collected. The dried product (15·7 g.) was distilled under reduced pressure and gave a pale yellow solid (11·3 g., 23·5%), b. p. 187—193°/2—3 mm. Although this material softened and melted over the range 120—140°, it gave very satisfactory results in the next stage of the synthesis. After two crystallisations from 80% ethyl alcohol yellow needles, m. p. 140°, were obtained (Found: C, 78·4; H, 4·8; N, 16·7. Calc. for $C_{11}H_8N_2$: C, 78·6; H, 4·8; N, 16·7%). A large number of preparations gave yields of 22—26%, after distillation under reduced pressure.

5-Hydroxy-1-naphthonitrile.—A solution of 5-amino-1-naphthonitrile suitable for rapid diazotisation was prepared by dissolving the amine (5·04 g., 0·03 mole) in glacial acetic acid (60 ml.) at 80° and, while this was vigorously agitated, adding quickly 60 ml. of a 40% w/w solution of sulphuric acid at 80°. Stirring was continued while the mixture was cooled rapidly to 0°. A solution of sodium nitrite (4·2 g., 0·06 mole) in water (30 ml.) was then added at 0° and the mixture stirred at 0—5° until a clear solution was obtained. Urea was added in small portions until the solution was free from nitrite. The ice-cold diazonium solution was immediately added dropwise to a vigorously stirred and boiling solution of sulphuric acid (180 ml.; 40% w/w) in 30 min. Refluxing was continued for 1 hr., and the mixture cooled. Water (300 ml.) was added and the crystals and solution were extracted with ether. The ethereal layer was extracted twice with N-sodium hydroxide, and acidification gave a pink precipitate of *5-hydroxy-1-naphthonitrile* (4·3 g., 83%). One crystallisation from aqueous acetic acid (35 ml. of glacial acetic acid and 65 ml. of water) gave orange needles (3·36 g., 66—

67%), m. p. 204—206°. This material was converted into the acid, but two further crystallisations from aqueous acetic acid gave pale yellow needles, m. p. 209·5° (Found: C, 77·8; H, 4·1; N, 8·2. $C_{11}H_7ON$ requires C, 78·1; H, 4·1; N, 8·3%).

5-Hydroxy-1-naphthoic Acid.—5-Hydroxy-1-naphthonitrile (8·4 g.) was refluxed with a solution of potassium hydroxide (50 g. in 100 ml. of water) for 4—5 hr. On acidification of the diluted hydrolysate, the light brown 5-hydroxy-1-naphthoic acid (8·46 g., 90%), m. p. 238° (decomp.), was obtained. This product was used for the preparation of the ethers, since two crystallisations from water failed to raise the m. p.

The acetyl derivative crystallised from benzene in small, colourless plates, m. p. 204—205° (cf. Cason, *J. Amer. Chem. Soc.*, 1941, **63**, 830).

5-Methoxy-1-naphthoic Acid.—5-Hydroxy-1-naphthoic acid, in alkaline solution, was methylated with methyl sulphate at 40—60°. Any ester in the product was removed by 1 hour's refluxing with 10% methyl-alcoholic sodium hydroxide. The pale yellow methoxy-acid melted at 220—227°: after two crystallisations from 95% ethyl alcohol, and one sublimation at 190°/2 mm., it was obtained as colourless needles, m. p. 232·5° (Found: C, 71·3; H, 5·2. Calc. for $C_{12}H_{10}O_3$: C, 71·3; H, 4·9%).

5-n-Alkoxy-1-naphthoic Acids.—5-Hydroxy-1-naphthoic acid (1·88 g., 1 mol.), potassium hydroxide (0·7 g., 2 mols.), water (5 ml.), ethyl alcohol (40 ml.), and the *n*-alkyl halide (1·5 mols.) were refluxed (alkyl iodide, 8 hr.; alkyl bromide, 16 hr.). Aqueous potassium hydroxide (10 ml.; 10%) was added, and refluxing continued for 2 hr. to hydrolyse any ester. The *alkoxy-acids* were obtained as pure, colourless products after two crystallisations from glacial acetic acid, one from 95% ethyl alcohol, and, except in the case of the last three members of the following Table, one sublimation at 175—185°/2 mm. After the first crystallisation the acids were almost pure; the yields at this stage were 80—90%.

5-Alkoxy-1-naphthoic acids.

		Found (%)			Required (%)	
Alkyl	M. p.	C	H	Formula	C	H
Ethyl	201°	71·9	5·8	$C_{13}H_{12}O_3$	72·2	5·6
Propyl	189	72·9	5·9	$C_{14}H_{14}O_3$	73·1	6·1
Butyl	172	73·7	6·4	$C_{15}H_{16}O_3$	73·8	6·5
Pentyl	143	74·2	7·1	$C_{16}H_{18}O_3$	74·4	7·0
Hexyl	154	74·7	7·4	$C_{17}H_{20}O_3$	75·0	7·4
Heptyl	135·5	75·5	7·6	$C_{18}H_{22}O_3$	75·5	7·7
Octyl	142·5	75·9	7·9	$C_{19}H_{24}O_3$	76·0	8·0
Nonyl	143	76·4	8·3	$C_{20}H_{26}O_3$	76·4	8·3
Decyl	137	76·7	8·4	$C_{21}H_{28}O_3$	76·8	8·5
Dodecyl	125	77·4	9·0	$C_{23}H_{32}O_3$	77·5	9·0
Hexadecyl	117·5	78·6	9·8	$C_{27}H_{40}O_3$	78·6	9·7
Octadecyl	122	79·2	9·9	$C_{29}H_{44}O_3$	79·1	10·0

6-Bromo-2-naphthol.—Mossy tin was prepared in the following way. Stannous chloride (112 g., 0·5 mole) was dissolved in water (150 ml.), and zinc dust (30 g., 0·46 g.-atom) added with shaking. Heat was evolved and the mossy tin was precipitated immediately. When cold, the tin was filtered off, washed well with cold water, and dried under vacuum. The yield was approx. 55 g.

2-Naphthol (144 g., 1 mole) was suspended in glacial acetic acid (400 ml.) and brominated at room temperature. Without isolation, the 1 : 6-dibromo-2-naphthol was reduced to 6-bromo-2-naphthol by addition of successive quantities of mossy tin to the boiling solution (cf. *Org. Synth.*, 1940, **20**, 18). The product (214—223 g., 96—100%), m. p. 123—127°, was sufficiently pure for the next stage, although it contained some tin salts.

2-Bromo-6-methoxynaphthalene.—6-Bromo-2-naphthol with methyl sulphate in alkali (French and Sears, *J. Amer. Chem. Soc.*, 1948, **70**, 1279) gave the colourless ether, m. p. 103—105°, b. p. 189—199°/20 mm. (60—70%). One crystallisation from absolute ethyl alcohol gave colourless needles, m. p. 106—107°.

6-Methoxy-2-naphthoic Acid.—The Grignard compound from 2-bromo-6-methoxynaphthalene was prepared in ether–benzene and converted into the acid as described by Fries and Schimmelschmidt (*Ber.*, 1925, **58**, 2835). The crude acid was dissolved in hot N-sodium hydroxide, and the solution was filtered and acidified. The precipitate, crystallised from xylene, formed colourless needles, m. p. 206° (50—55%).

2-Acetyl-6-methoxynaphthalene.—This was prepared by the action of acetyl chloride on 2-bromo-6-methoxynaphthalene in the presence of anhydrous aluminium trichloride in nitro-

benzene (Robinson and Rydon, *J.*, 1939, 1399). Distillation of the product under reduced pressure (b. p. 165—170°/3—4 mm.) and crystallisation from methanol gave colourless blades (50%), m. p. 104—105°.

6-*Methoxy*-2-*naphthoic Acid*.—A solution of sodium hypobromite, prepared from sodium hydroxide (140 g.), water (600 ml.), and bromine (50 ml.) at 0—5°, was added dropwise to a stirred solution of the 2-acetyl-6-methoxynaphthalene (50 g.) in dioxan (350 ml.) during 30 min., the temperature being kept at 35—40°, but later raised to 50—55° to ensure complete oxidation. Excess of bromine was destroyed with sodium dithionite, and the mixture was diluted with water (2 l.). After the dioxan and bromoform had been removed by steam-distillation, the hot alkaline solution was filtered. Acidification with concentrated hydrochloric acid yielded the pale yellow acid (48·7 g.); one crystallisation from xylene gave colourless needles of 6-methoxy-2-naphthoic acid, m. p. 205—206° (35—37 g., 70—75%).

6-*Hydroxy*-2-*naphthoic Acid*.—6-Methoxy-2-naphthoic acid (8·4 g.) was heated for 2·5 hr. with acetic acid (35 ml.), 48% hydrobromic acid (35 ml.), and glacial acetic acid (20 ml.) saturated with hydrogen bromide, the methoxy-acid dissolving. The dark solution was cooled, and the light brown crystals were collected and washed with water. One crystallisation from water (1·2 l.) gave pale tan needles (69—75%), m. p. 250° (Found: C, 70·2; H, 4·2. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%).

The *acetyl* (Found: C, 67·7; H, 4·2. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·35%) and *benzoyl* (Found: C, 74·1; H, 4·0. $C_{18}H_{12}O_4$ requires C, 74·0; H, 4·1%) derivatives crystallised from ethyl acetate in very small needles, m. p. 228° (decomp.) and 257° respectively. For the *benzenesulphonyl* derivative (Found: C, 62·2; H, 3·8. $C_{17}H_{12}O_5S$ requires C, 62·2; H, 3·7%) the m. p. was 228·5° after crystallisation from acetic acid.

6-n-*Alkoxy*-2-*naphthoic Acids*.—6-Hydroxy-2-naphthoic acid was alkylated in the same way as 5-hydroxy-1-naphthoic acid. After one crystallisation from glacial acetic acid the ethers were obtained as colourless needles in 85—90% yield and crystallised twice from glacial acetic acid and twice from xylene (see Table).

6-Alkoxy-2-naphthoic acids.

		Found (%)			Required (%)	
Alkyl	M. p.	C	H	Formula	C	H
Methyl	206°	71·2	5·0	$C_{12}H_{10}O_3$	71·3	4·9
Ethyl	213	72·3	5·4	$C_{13}H_{12}O_3$	72·2	5·6
Propyl	208	72·9	6·1	$C_{14}H_{14}O_3$	73·1	6·1
Butyl	198	73·9	6·4	$C_{15}H_{16}O_3$	73·8	6·5
Pentyl	179·5	74·3	6·9	$C_{16}H_{18}O_3$	74·4	7·0
Hexyl	147	74·9	7·4	$C_{17}H_{20}O_3$	75·0	7·4
Heptyl	163	75·1	7·7	$C_{18}H_{22}O_3$	75·5	7·7
Octyl	161·5	75·9	8·0	$C_{19}H_{24}O_3$	76·0	8·0
Nonyl	147·5	76·6	8·4	$C_{20}H_{26}O_3$	76·4	8·3
Decyl	139	76·8	8·6	$C_{21}H_{28}O_3$	76·8	8·5
Dodecyl	119	77·4	9·1	$C_{23}H_{32}O_3$	77·5	9·0
Hexadecyl	107	78·9	9·7	$C_{27}H_{40}O_3$	78·6	9·7
Octadecyl	114	79·2	9·9	$C_{29}H_{44}O_3$	79·1	10·0

6-iso*Pentyloxy*-2-*naphthoic acid*, crystallised thrice from acetic acid, had m. p. 194° (Found: C, 74·3; H, 7·0. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

6-(3 : 5 : 5-*Trimethylhexyloxy*)-2-*naphthoic acid*, similarly crystallised, had m. p. 170° (Found: C, 76·6; H, 8·2. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%).

7-*Amino*-2-*naphthonitrile*.—7-Aminonaphthalene-2-sulphonic acid (35 g.) and potassium cyanide (70 g.) were dry-distilled, and the product was treated in the same way as that from 5-amino-1-naphthonitrile. Precipitation with ammonia gave the amine (3·3 g.), m. p. 140—160°. One crystallisation from benzene or absolute ethyl alcohol gave pale yellow needles, m. p. 194—196° (1·7 g., 7·1%). This material was pure enough for the conversion into the hydroxy-nitrile. Two further crystallisations from benzene raised the m. p. to 197° (Found: C, 78·4; H, 4·8; N, 16·7. Calc. for $C_{11}H_8N_2$: C, 78·6; H, 4·8; N, 16·7%).

7-*Hydroxy*-2-*naphthonitrile*.—7-Amino-2-naphthonitrile was diazotised and hydrolysed to give the hydroxy-nitrile in the same manner as 5-hydroxy-1-naphthonitrile. One crystallisation from 35% acetic acid gave orange-yellow plates, m. p. 183—185° (76%). Two further crystallisations from the same solvent yielded pale yellow plates, m. p. 186·5° (Found: C, 78·1; H, 4·1; N, 8·2. $C_{11}H_7ON$ requires C, 78·1; H, 4·1; N, 8·3%).

7-*Hydroxy*-2-*naphthoic Acid*.—7-Hydroxy-2-naphthonitrile (2·5 g.) was heated in 2N-potassium hydroxide (50 ml.) until ammonia was no longer evolved (4—5 hr.). The solution

was cooled, diluted with an equal volume of water, and acidified with concentrated hydrochloric acid, giving 7-hydroxy-2-naphthoic acid as a pale pink solid (2·4 g., 90%), m. p. 266—269°. This material was used for the alkylations. Two crystallisations from water gave pale yellow needles, m. p. 269—270° (Found: C, 70·1; H, 4·4. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%).

The 7-*n*-alkoxy-2-naphthoic acids were prepared in the same way as the 5-alkoxy-1-naphthoic acids.

7-n-*Octyloxy*-2-*naphthoic acid*, obtained in 90% yield after one crystallisation from glacial acetic acid, formed pale yellow needles, m. p. 139·5—141·5°. Further crystallisations from 90% ethyl alcohol and xylene raised the m. p. to 141·5°, but failed to remove all the colour. Colourless prisms were obtained by sublimation at 170°/2—3 mm., and had m. p. 142·5° (Found: C, 76·0; H, 7·9. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·0%).

7-n-*Hexadecyloxy*-2-*naphthoic acid* (90% yield) was similarly obtained colourless only on sublimation at 210—220°/4 mm., forming needles, m. p. 138° (Found: C, 78·6; H, 9·7. $C_{27}H_{40}O_3$ requires C, 78·6; H, 9·7%).

Grateful acknowledgment is made to the Distillers Co., Ltd., and to Imperial Chemical Industries Limited for grants to the Department.

UNIVERSITY COLLEGE, HULL. [*Received, October 31st*, 1953].

Mesomorphism and Chemical Constitution. Part I. The n-*Alkoxynaphthoic Acids.*

By G. W. GRAY and BRYNMOR JONES.

[Reprint Order No. 4761.]

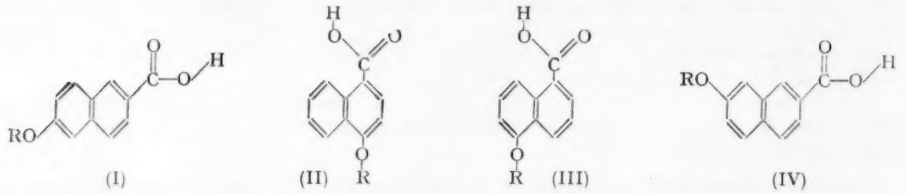
4- and 5-*n*-Alkoxy-1-naphthoic acids, and the 7-*n*-alkoxy-2-naphthoic acids exhibit no mesophases, whereas 6-*n*-alkoxy-2-naphthoic acids are mesomorphic. These results are discussed in relation to the structures of the acids, and the mesomorphic naphthoic acids are compared with the *p*-*n*-alkoxybenzoic acids and *trans*-*p*-*n*-alkoxycinnamic acids.

ALTHOUGH many mesomorphic compounds have been reported, little is known of the effect of changes in molecular constitution and shape on the degree of anisotropy in the melt. Inspection of the formulæ of mesomorphic compounds makes it clear that all the molecules are characterised by their predominant length. The molecules have a rod shape, which favours the linear molecular arrangement proposed by Friedel (*Ann. Physique*, 1922, **18**, 273) for the smectic and the nematic state. Such molecules will have a strong tendency to lie with their long axes parallel, and this will be accentuated by any dipoles in the molecule. Only few molecules broader than benzene have been found to be mesomorphic (Vorländer, *Trans. Faraday Soc.*, 1933, **29**, 907), and insufficient evidence exists to show what effect increase in breadth has on mesomorphism. One of the few established facts is that a nematic phase of 27° in *p*-*n*-pentyloxybenzoic acid is eliminated by 3 : 5-dichlorination—here a substantial increase in breadth destroys the mesomorphism.

More is known about the general effect of systematic increments in molecule length. Bennett and Brynmor Jones (*J.*, 1939, 420) and Weygand *et al.* (*J. pr. Chem.*, 1940, **155**, 332, *Ber.*, 1938, **71**, 2399; *Naturwiss.*, 1931, 27, 28) prepared homologous series of *n*-alkoxy-compounds, *e.g.*, *p*-*n*-alkoxybenzoic acids, *trans*-*p*-*n*-alkoxycinnamic acids, and homologues of *p*-azoxy- and *p*-azo-anisole. These investigations show that when the alkyl chains are short the systems are either non-mesomorphic or nematic. As the chain length is increased, smectic properties begin to appear, and, as the smectic phase lengths increase, the nematic phase lengths decrease with each successive chain increment, until in the hexadecyl and the octadecyl ethers smectic phases alone are usually found. Among these systems no systematic effect of chain length on phase length was observed.

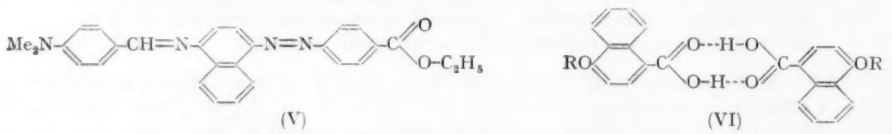
In an endeavour to enlarge the existing knowledge of the effect of breadth on mesomorphism, the alkoxynaphthoic acids were examined. These were chosen for their similarity in molecular constitution to the series studied by Bennett and Jones (*loc. cit.*), and because alterations in the relative positions of the alkoxy- and the carboxy-group

change the effective molecular breadths and the linearity of the molecules. A brief preliminary report of the general behaviour of some of these acids has already been made (Gray and Brynmor Jones, *Nature*, 1951, **167**, 83). Four types have now been examined, and of these the 6-*n*-alkoxy-2-naphthoic acids (I) alone are mesomorphic, whereas the 4- (II) and the 5-*n*-alkoxy-1-naphthoic acids (III) and the 7-*n*-alkoxy-2-naphthoic acids (IV) are not mesomorphic. For the last two this may be attributed to the fact that the



(I) (II) (III) (IV)

molecules are not rod-shaped, since the axes of carboxy- and alkoxy-groups are not in line. This is particularly true when the dimer is considered. The 4 : 1-acids are essentially linear, but they are also very broad. Nevertheless, Vorländer (*loc. cit.*) has reported that ethyl 4′-*p*-dimethylaminobenzylideneamino-1′-naphthylazobenzoate (V), which is the same breadth, is mesomorphic. On this basis, these acids might be expected to show mesophases, particularly as their melting points are lower in seven cases than the upper clearing point of 197° for (V). It is possible that the acid dimer, which will be the effective unit in the crystal lattice, is as in (VI). This represents a molecule which is half as broad again as (V), which contains only one naphthalene ring. However, even if the dimer is the same breadth as (V), mesomorphism may be made impossible by the fact that the two naphthalene rings cause such imbrication in the molecule that the closest packing in the crystal lattice is not one in which the molecules lie parallel.



(V) (VI)

The mesomorphism of the 6-*n*-alkoxy-2-naphthoic acids is however to be expected, since the molecules and the dimers, although broader than the *p*-*n*-alkoxybenzoic acids, are both long and rod-shaped. Furthermore, the molecules are very similar in shape to the *trans*-*p*-*n*-alkoxycinnamic acids which are mesomorphic (Bennett and Brynmor Jones, *loc. cit.*).

These results make it highly improbable that any other *n*-alkoxy-1- or -2-naphthoic acid would exhibit mesomorphism, since any other relative distribution of alkoxy- and carboxy-groups would result in even greater deviations from linearity. The molecules would indeed be similar to *o*- or *m*-alkoxybenzoic acids, which show no mesophases.

The thirteen 6-*n*-alkoxy-2-naphthoic acids (methyl–decyl, dodecyl, hexadecyl, and octadecyl) are mesomorphic. The usual behaviour of a homologous series is shown by the fact that the lower members (methyl–octyl) are nematic, while the intermediate members exhibit both phase types, and the higher ethers (hexadecyl and octadecyl) are purely smectic. The corrected melting points, the smectic–nematic, and the smectic– and nematic–isotropic transition points are tabulated below.

As is true to a lesser extent in the corrected constants for the *p*-*n*-alkoxybenzoic acids (Gray and Brynmor Jones, *J.*, 1953, 4179), fluctuations and an absence of regularity are observed in the nematic and in the overall phase lengths along the series. In both series however, after the onset of smectic properties, the nematic phase length decreases gradually to zero as the smectic phase length increases. The only exception to this is the octadecyl ether, which, compared with the hexadecyl ether, has a reduced phase length. The smectic phase of the nonyl ether is monotropic: that is, the solid melts at 147·5° to the nematic state, but, on cooling, passes through a smectic phase which appears at 140°

Alkyl group	Temp. of transition to smectic	nematic	isotropic	Phase length of smectic	nematic
Methyl	—	206°	219°	—	13°
Ethyl	—	213	224	—	11
Propyl	—	208	208·5	—	0·5
Butyl	—	198	208·5	—	10·5
Pentyl	—	179·5	199	—	19·5
Hexyl	—	147	198·5	—	51·5
Heptyl	—	163	192	—	29
Octyl	—	161·5	190	—	28·5
Nonyl	(140°)	147·5	183·5	(7·5°)	36
Decyl	139	147	181	8	34
Dodecyl	119	158·5	174	39·5	15·5
Hexadecyl	107	—	160·5	53·5	—
Octadecyl	114	—	159	45	—

just before the crystals of the solid appear. In the Table, the transition of 140° and the phase length of 7·5° are in parentheses, since they relate to a monotropic effect; the length of the phase is indeed a negative amount relative to the lengths of the enantiotropic phases.

In both series, when the constants are plotted against the number of carbon atoms in the alkyl chain, the upper transition points lie on two smooth curves, the upper curve corresponding to the acids with an even number of carbon atoms in the alkyl chain, and the lower to those with an odd number. This behaviour is common to many homologous series where the molecules pack together so that their long axes are parallel. It is believed that the alternations arise through variations in the packing of the terminal methyl group for odd and even members (Malkin, *Trans. Faraday Soc.*, 1933, **29**, 977).

Since only these general similarities between the two series may be admitted, it is now necessary to compare the different series more specifically: that is, a criterion of the degree of mesomorphism is essential so that it may be decided which of two series is the more mesomorphic. The length of a phase is an unsuitable measure of mesomorphism since it indicates only the degree of separation of the lower m. p. and the upper transition point. The m. p. does determine the temperature at which the mesophase appears, but is a measure of the stability of the crystal lattice rather than of that of the mesophase. Two very similar compounds, which would be expected to have similar degrees of mesomorphism, may give widely different phase lengths because their crystal types and their internal energies are not the same, and give rise to different m. p.s. This means that the m. p. may be affected by the crystal type, and by polymorphic changes which are quite unrelated to the stability of the mesophase. Such factors may vary along a homologous series and result in irregularity of both m. p. and phase length. This in fact is most often the case. The phase length is therefore an unreliable criterion because of the influence of external factors upon the m. p. Objections of this kind do not apply to the upper transition points, which determine the temperature at which the thermal agitation destroys the linear orientation of the mesophase, through weakening of the intermolecular forces. This temperature is a direct measure of the stability of the mesophase. Therefore, a compound of m. p. 150° and upper clearing point 250° is less mesomorphic than another of m. p. 250° and upper clearing point 251°, since the phase of the latter is capable of resisting thermal breakdown at a higher temperature. This criterion of greater or smaller degrees of mesomorphism has been used in the comparison of the relative behaviours of many mesomorphic compounds.

From the Table it is clear that the most mesomorphic member is 6-ethoxy-2-naphthoic acid, with upper transition point 224°. In this series the general trend is for the upper transition points, and consequently the mesomorphism, to decrease as the alkyl chain length increases. Such behaviour may result from a decrease in intermolecular cohesion per unit length of the molecule as the chain length increases and the system becomes more paraffinic in character. The result will be a reduced thermal stability of the mesophase. Thus, mesomorphism decreases with increasing molecular length along a homologous series, since the cohesion is not maintained in proportion as the length is increased. This occurs with a general increase in phase length, which is therefore an unreliable guide to mesomorphic behaviour.

When the smectic–nematic and the smectic–isotropic transitions are plotted against the number of carbon atoms in the chain, the points are found to lie on a smooth curve

which rises to the smectic–isotropic transition at 160·5° of the hexadecyl ether. Since the stability of the smectic phase cannot increase indefinitely, the curve then falls slightly to 159°, the smectic–isotropic transition for the octadecyl ether. This decrease is in keeping with the general decrease in mesomorphic stability along the series. In the *p*-*n*-alkoxybenzoic acids, the smectic–nematic and the smectic–isotropic transitions also lie on a smooth curve, which rises from heptyl to hexadecyl and then falls slightly to octadecyl.

The upper transition points for 6-*n*-alkoxy-2-naphthoic acids are higher than those for *p*-*n*-alkoxybenzoic acids with the same alkyl groups, by an average of 47°, and the former are therefore the more mesomorphic. Thus, despite their smaller molecular breadths (6·8 Å) the benzoic acids are less mesomorphic than the naphthoic acids (breadth 7·9 Å). Moreover, the molecules of the naphthoic acids are longer by 2·2 Å, but, unlike the increases in a homologous series, this greater length results from the presence of the second aromatic ring of the naphthalene nucleus. This will contribute more to the intermolecular cohesion than a single benzene ring, and so enhances the thermal stability. The effect is made clear by comparing members of each series in which molecule lengths are approximately the same. For example, 6-ethoxy-2-naphthoic acid (length 14·3 Å), upper transition point 224°, is considerably more mesomorphic than *p*-*n*-pentyloxybenzoic acid (length 14·82 Å), upper transition point 151°.

For the same reasons, the *trans*-*p*-*n*-alkoxycinnamic acids are more mesomorphic than the *p*-*n*-alkoxybenzoic acids, whereas the 6-*n*-alkoxy-2-naphthoic acids are more mesomorphic than the cinnamic acids. Naphthoic and cinnamic acids containing the same alkyl group will be of the same length, and the greater mesomorphism of the former must be due to the presence of the second aromatic ring of the naphthalene nucleus compared with the ethylenic bond in the cinnamic acids.

Experimental.—The physical constants for the 6-*n*-alkoxy-2-naphthoic acids were obtained in an electrically heated instrument (Gray, *Nature*, **1953**, **172**, 1137), and are corrected for exposed stem. Enantiotropic polymorphic transitions were also determined with this instrument; the following data were obtained, the stable solid at room temperature being termed solid I.

The butyl and pentyl ethers exhibit a monotropic polymorphic transition.

Alkyl group	Heptyl	Octyl	Nonyl
Transition of solid I to solid II	105°	160·5°	115°

In polarised light, the nematic phases in all cases were highly threaded or were made up of homogeneous areas which contained threads. The smectic phases did not give well-defined focal-conic groups, but appeared as fine, mottled mosaics consisting of minute focal-conics.

UNIVERSITY COLLEGE, HULL. [*Received, October* 31*st*, 1953.]

The Conductivity of Electrolytes in Non-aqueous and Mixed Solvents. Part I.

By V. S. GRIFFITHS.

[Reprint Order No. 4600.]

Measurements of the conductivity of silver nitrate in binary mixtures of acetone–water, 1 : 4-dioxan–water, pyridine–water, and ethanol–pyridine over the complete solvent mixture concentration range are reported and discussed.

THE variation of the conductivity of electrolytes with solvent composition has been extensively investigated by a variety of methods and techniques. Ives (*J.*, 1933, 1360) has shown that much information can be obtained about the behaviour of electrolytes in water-rich aqueous pyridine mixtures, and his simple titration technique was essentially the method used in this work. The electrolyte most used was silver nitrate, because it is reasonably soluble in a variety of non-aqueous solvents, and it is known that Ag^+ interacts

strongly with certain organic molecules owing to its electron-accepting properties. Indeed, Kraus and Burgess (*J. Amer. Chem. Soc.*, 1948, **70**, 706) conclude from their work in a variety of solvents that the silver ion is exceptional in this respect. Thus by choosing a solvent with electron-donating powers it is possible to obtain a system wherein the cation is likely to be preferentially and very strongly solvated. For instance, if the solvent is pyridine, then the existence of complex ions of the type $Ag(py)_2^+$ (Woodman and Corbett, *J.*, 1925, **127**, 2461; Schmidt and Keller, *Z. physikal. Chem.*, 1929, **141**, *A*, 331; Britton and Williams, *J.*, 1935, 798) and $Ag(py)^+$ (Vosburgh and Cogswell, *J. Amer. Chem. Soc.*, 1943, **65**, 2412) demonstrates extremely strong cation–solvent interaction. The formation of large singly-charged ions is likely to discourage further solvation. Further, Ulich (*Trans. Faraday Soc.*, 1927, **23**, 388) has shown that the anion is little solvated with pyridine, so that, for the purpose of this work, this system may be regarded as a limiting case of " cationic solvation." It was thought that if the conductivities of silver nitrate in pyridine–water mixtures were compared with the conductivities in aqueous solutions of other solvents possessing electron-donating properties, some indication of the relative cation–solvent interaction would be obtained. The solvents used were 1 : 4-dioxan and acetone, and, for further comparison, ethanol, the last being assumed to solvate both anion and cation. Consequently, the effect of adding pyridine, 1 : 4-dioxan, acetone, and ethanol to aqueous solutions, and pyridine to ethanolic solutions, of silver nitrate, the concentration of electrolyte being kept constant, has been studied and the results for 0·0005M-solutions are shown graphically. Other concentrations of electrolyte (0·0003 and 0·0008M) were also used but the essential character of the curves was the same.

Results

Generally, the results are shown in graphical form, but two sets of typical results are shown in the Table. From large-scale plots, equivalent conductivities, fluidities, and dielectric constants were interpolated at any required solvent composition, and thus any derived quantity was calculated.

Equivalent conductivities of 0·0005M-$AgNO_3$ *in mixed solvents.*

(*a*) C_5H_5N–H_2O

C_5H_5N, mol. %	Λ	C_5H_5N, mol. %	Λ	C_5H_5N, mol. %	Λ
0·000	131·36	0·139	98·81	0·387	95·31
0·003	130·50	0·163	97·93	0·524	93·56
0·036	104·71	0·196	97·50	0·584	93·34
0·094	99·46	0·257	96·84	1·007	88·31

(*b*) C_2H_5·OH–H_2O

C_2H_5·OH, mol. %	Λ	C_2H_5·OH, mol. %	Λ	C_2H_5·OH, mol. %	Λ
0·000	131·36	2·035	112·49	12·58	68·95
0·318	130·80	4·435	97·32	20·25	56·89
1·328	120·30	10·46	71·89		

Discussion

Fig. 1 shows the equivalent conductivity of 0·0005M-silver nitrate corrected for viscosity changes ($\Lambda\eta/\eta_0$) plotted against mol. % of one component of the solvent mixtures, and the curves fall into two groups, one of which is made up of the mixtures containing pyridine as a component.

The initial effect of adding pyridine to an aqueous solution of silver nitrate is a sharp decrease of $\Lambda\eta/\eta_0$, which can be attributed to the formation of a complex cation of reduced mobility as compared with the silver ion. Once this change is complete, then $\Lambda\eta/\eta_0$ shows relatively little change over the rest of the composition range. This implies that the dissociation remains complete and that the conductivity remains essentially a function of the fluidity of the medium, in spite of the decreasing dielectric constant. The behaviour of potassium chloride and nitrate in similar solvent mixtures is quite different from that of silver nitrate in so far as $\Lambda\eta/\eta_0$ shows a reasonable constancy up to a considerable pyridine concentration (see Fig. 2) and lends strong support to the formation of the complex ion in the case of silver nitrate. The general conclusions are summarised in Fig. 5, which shows the relative conductivities, fluidities, and dielectric constants (*i.e.*, the ratio of the physical quantity concerned in mixed and pure solvents) plotted against solvent composition.

The initial addition of pyridine to ethanolic solutions causes an abrupt, but not large,

increase in $\Lambda\eta/\eta_0$ which cannot reasonably be attributed to an increase in ionic mobility. It seems probable that the effect is a result of more than one process. It is to be expected that a complex cation will be formed, as in water, of reduced mobility. The resulting fall in conductivity is more than nullified by some larger effect operating in the opposite sense. It is suggested that this is an increase in dissociation of the electrolyte, since silver nitrate is only about 92% dissociated in ethanol at the concentration concerned (see Davies, "Conductivity of Solutions," 2nd Edn., Chapman and Hall, 1933, p. 118), and, when the larger complex cation is formed, the dissociation proceeds to completion. Again, in this

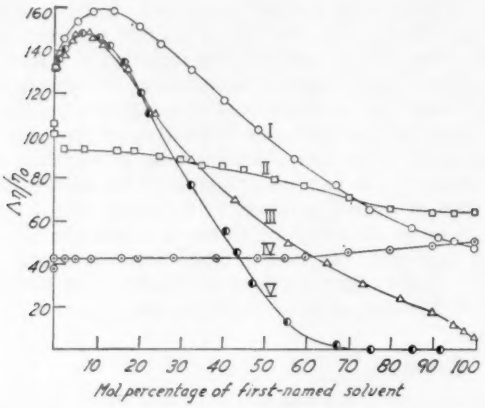


FIG. 1. *Conductivity of silver nitrate* (0·0005M) *in mixed solvents.*

I, Ethanol–water.
II, Pyridine–water.
III, Acetone–water.
IV, Pyridine–ethanol.
V, Dioxan–water.

Viscosity-corrected equivalent conductivities of various salts (0·0005M).

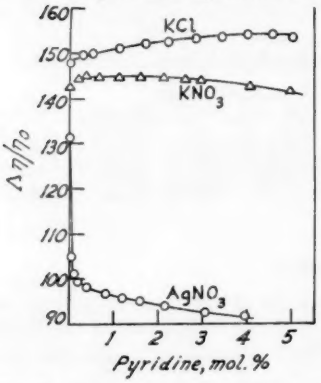


FIG. 2. *In pyridine–water mixtures.*

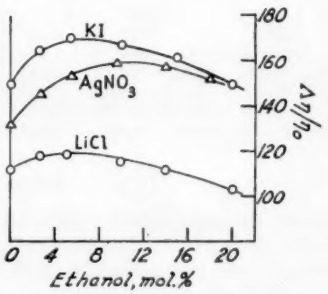


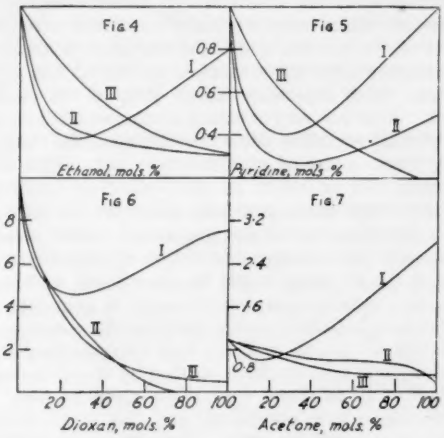
FIG. 3. *In ethanol–water mixtures.*

system, after the establishment of the fully dissociated complex as the real solute, the conductivity remains essentially a function of the fluidity of the medium over a very considerable solvent composition range, as is shown by Fig. 8.

The other systems, *viz.*, aqueous ethanol, dioxan, and acetone, show an interesting common feature. This is a maximum in $\Lambda\eta/\eta_0$ at approximately 10 mol. % of organic solvent, followed by a smooth fall over the remainder of the concentration range. In aqueous dioxan, the conductivity becomes almost negligible above 70 mol. % of dioxan. The reason for this behaviour is not clear but the following explanation is suggested.

The initial rise to the maximum value of $\Lambda\eta/\eta_0$, which has also been observed for potassium iodide and lithium chloride (see Connell, Hamilton, and Butler, *Proc. Roy. Soc.*, 1934, **147**, *A*, 418, and Fig. 3), cannot be due to an increase of dissociation because, for these

solutes, dissociation is complete in water. It would seem reasonable to exclude complex formation, which would tend to affect the results in the opposite direction, and the increase in $\Lambda\eta/\eta_0$ must, therefore, be due to an increase in ionic mobility of a kind which is not a function of the fluidity of the bulk medium. The effect can be explained in terms of solvation of the ions, which, in a mixed solvent, may occur differentially. On general grounds it appears probable that, of the solvents concerned, water will have the greatest tendency to solvate the cations, so that the cation will be preferentially hydrated (*e.g.*, see, Shaw and Butler, *ibid.*, 1930, **129**, *A*, 519). Now the solvation, at least in the outer reaches, may be regarded as purely electrostatic in origin, in the sense that the intensely inhomogeneous field of the ion will cause the greater attraction for the more polar component of the mixture. Thus, proceeding outwards from the ion it is to be expected



Relative fluidity (I), *conductivity* (II), *and dielectric constant* (III) *curves for* 0·0005M-$AgNO_3$ *solutions in mixed solvents.*

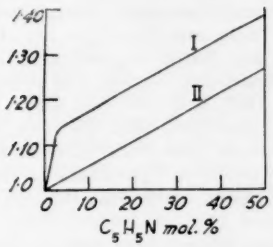


FIG. 8. *Relative conductivity* (I) *and fluidity* (II) *curves of* 0·0005M-$AgNO_3$ *solutions in ethanol–pyridine mixtures.*

that there will be a change in the composition of the medium, which is predominantly aqueous at first, followed by regions where the concentration of organic solvent increases, until the bulk composition is reached. Now if, when the ion moves under the influence of the applied field, the " surface of shear " is closer to the ion than the region at which the bulk composition is attained, the shearing process, on which the ionic mobility partly depends, will be marked by a fluidity characteristic of a more aqueous medium than that of the bulk mixture. For all the mixed solvents concerned, there is an initial decrease of relative fluidity as the concentration of the organic component increases (see Figs. 4—7), and it is noteworthy that ethanol shows the lowest value of relative fluidity and the highest maximum in $\Lambda\eta/\eta_0$. It is possible that the same effect may operate in the reverse direction when the fluidity minimum has been passed.

As the concentration of the non-aqueous component increases, the decrease in the bulk dielectric constant will begin to play a major part, and the gradual decrease in $\Lambda\eta/\eta_0$ can be explained by assuming that increasing association of the electrolyte is occurring.

Experimental

Procedure.—Conductivity measurements were made at 25° with the apparatus described by Davies (*J.*, 1937, 432). " Air-tight " all-glass borosilicate glass cells were used. The titration technique described by Ives (*loc. cit.*) was used for the most part. 0·0005M-Solutions in mixed solvents of known composition were made up in all-glass apparatus and a known weight of solution was blown over into the cell by means of dry nitrogen. Weighed quantities of 0·0005M-electrolyte solutions in one component of the binary mixture were added, and the cell resistance was measured after each addition. Volume changes were corrected for by adding calculated amounts of the mixed solvents, although if the change was not large it was found that the results could be corrected by multiplying the cell resistance by the ratio of real volume to total volume of cell contents plus the volume added. The results were checked by making single observations on 0·0005M-solutions in solvents of known composition.

Solvent resistances for solvent correction were obtained from runs on mixed solvents in the absence of electrolytes, and the corrections obtained were usually small. However, in solutions containing pyridine the maximum correction was approximately 7×10^{-6} ohm^{-1} at 2 mol. % of pyridine, which represents about 10% of the conductivity of 0·0005M-silver nitrate in that solvent. Ives (*loc. cit.*) obtained similar results and stated that, although the correction applied is not strictly accurate, yet it is probably of the right order, since most of the solutions contained a very large excess of pyridine over salt. This, of course, implies that the addition of the electrolyte has no effect on the ionisation equilibrium of the aqueous pyridine solution, a situation which might not hold owing to the salting-out effect of the added ions. However, from a consideration of the magnitude of the conductivity changes on the addition of silver nitrate, and the relative quantities of electrolyte and solvent present, it would seem that although the accuracy might be questioned, and no claim is made for great accuracy, yet the application of such a correction is right in principle.

Materials.—Good-quality conductivity water was used of specific conductivity better than 0·8 gemmho. All electrolytes were recrystallised several times from conductivity water.

All organic solvents were purified by methods described by Griffiths (*J.*, 1952, 1326), and the densities of all mixtures were those given by him. Other physical constants of the mixtures were obtained from sources shown. (*a*) Pyridine–water mixtures: fluidities, Dunstan, Thole, and Hunt (*J.*, 1907, **91**, 1728; 1908, **93**, 561) and Hartley, Thomas, and Applebey (*J.*, 1908, **93**, 538); dielectric constants, Ives (personal communication). (*b*) Pyridine–ethanol mixtures: Dunstan, Thole, and Hunt (*loc. cit.*, 1907). (*c*) Ethanol–water mixtures: fluidities, Connell, Hamilton, and Butler (*loc. cit.*) and Bingham and Jackson (*Bull. Bur. Stand.*, 1918, **14**, 59); dielectric constants, Harned and Owen (" The Physical Chemistry of Electrolytic Solutions," 2nd Edn., 1950, Reinhold Publ. Corp., p. 118). (*d*) Dioxan–water mixtures: fluidities, Geddes (*J. Amer. Chem. Soc.*, 1933, **55**, 1019) and Owen and Waters (*ibid.*, 1938, **60**, 2371); dielectric constants, *idem* (*ibid.*) and Akerlof and Short (*ibid.*, 1936, **58**, 1241). (*e*) Acetone–water mixtures: fluidities, " International Critical Tables," McGraw-Hill, 1929; dielectric constants, Akerlof (*J. Amer. Chem. Soc.*, 1932, **54**, 4125) and Harned and Owen (*op. cit.*).

Battersea Polytechnic, London, S.W.11. [*Received, August 20th*, 1953.]

Studies in Spectroscopy. Part VI. Ultra-violet and Infra-red Spectra of Nitrosamines, Nitrites, and Related Compounds.*

By R. N. Haszeldine and J. Jander.

[Reprint Order No. 4806.]

The ultra-violet and infra-red spectra of nitrosamines and nitrites have been recorded and are compared with the spectra of other compounds containing nitrogen and oxygen. Nitrosamines are characterised by a low-intensity maximum at *ca.* 365 mμ which shows fine structure, and a high-intensity maximum at *ca.* 235 mμ. The marked effect of solvent on the spectrum readily distinguishes nitrosamines from nitrites, which also show multiple absorption in the 310—400-mμ region. Nitrites are characterised in the infra-red by three strong bands at 5·8, 6·1, and 6·2 μ and by a strong band *ca.* 12·5 μ; rotational isomerism is indicated. Nitrosamines show three characteristic bands: 7·1—7·4 μ (N:O), *ca.* 8 μ, and *ca.* 9·5 μ (N–O).

In connection with studies on polyhalogeno-compounds containing nitrogen reported in other series, the ultra-violet and infra-red spectra of nitrosamines, nitrites, and related compounds have been measured or correlated.

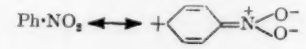
Monomeric *C*-nitroso-compounds are characterised by absorption at 650—700 mμ (Anderson and Hammick, *J.*, 1935, **30**; Anderson, Crumpler, and Hammick, *J.*, 1935, 1680), which is substantially independent of R in $R_3C{\cdot}NO$. The ultra-violet spectra of *C*-nitroalkanes are characterised by a band of low intensity near 280 mμ (see Figure; Haszeldine, *J.*, 1953, 2525) whose position moves only slightly with change of R in $R{\cdot}NO_2$, even when R contains fluorine. The spectra of nitrites differ greatly from those of the isomeric nitro-compounds (see Table 1 and Figure; for earlier work see Kuhn and Lehmann, *Z. physikal. Chem.*, 1932, **18**, *B*, 32 *et seq.*; 1935, **29**, *B*, 1) and resemble more the *C*-nitroso-compounds. This can be correlated with the ability of the nitroso-group to partake in resonance of the $^{+}X{=}N{-}O^{-}$ type, where X is an atom carrying a lone pair of electrons, *e.g.*, O, N, or Cl: $RO{\cdot}N{=}O \longleftrightarrow R{\cdot}\overset{+}{O}{=}N{\cdot}O^{-}$. The spectrum is substantially independent of R, since nitrous acid and its salts (Kortüm, *ibid.*, 1939, **43**, *B*, 418) and alkyl nitrites (Table 1) have essentially the same spectrum, with multiple absorption in the region 310—400 mμ. Unlike the nitrosamines (see below), the nitrites have identical spectra in light petroleum and in ethanol, and this enables the compounds to be distinguished. In a nitro-compound, *i.e.*, where R is now attached to the nitrogen atom of the N–O system, resonance of the above type cannot occur, and even if R is replaced by R'O to give a nitrate $R'O{\cdot}NO_2$, the extra oxygen atom cannot partake in resonance, and there is only a slight change in spectrum (see Figure; Haszeldine, *loc. cit.*).

The nitrogen atom of the nitroso-group in nitrosamines can partake in resonance involving the electrons of the adjacent nitrogen atom: $R_2N{\cdot}N{=}O \longleftrightarrow R_2N^{+}{=}N{-}O^{-}$. In light petroleum solution the ultra-violet spectrum thus resembles that of a nitrite, or that of nitrosyl chloride vapour. The low-intensity long-wave-length maximum at *ca.* 365 mμ shows fine structure (see Figure and Table 1), and there is a high-intensity maximum at short wave-length (235 mμ; cf. BuO·NO, 220 mμ) which is similar to that for a nitramine. Nitrosamines are readily distinguished from nitrites by the marked shift to the blue (15 mμ), with loss of fine structure, which occurs when the solvent is changed to ethanol (see Figure). The position and intensity of the short-wave-length maximum remains unchanged, and there is little difference between spectra in a homologous series.

Nitramines are colourless compounds and there is no maximum or inflection in their spectra at wave-lengths >260 mμ; they are characterised by a high-intensity absorption band in the region 230—250 mμ (Table 1). The difference in spectrum between a nitramine and a nitrosamine is thus as marked as that between a *C*-nitro-compound

* Part V, *J.*, 1953, 2622.

and a nitrite, since again resonance of the type $^{+}X{=}N{-}O^{-}$ cannot occur to any extent even though X (= N in $R_2N{\cdot}NO_2$) is co-ordinatively unsaturated. Compounds $R{\cdot}NO_2$ show long-wave-length absorption only when R is covalently unsaturated, *e.g.*,



The ultra-violet spectrum of only one *ON*-dialkyl-*N*-nitrosohydroxylamine has been reported (Table 1). The β-methyl ester of the so-called " Traube compound " [*i.e.*, $MeO{\cdot}N(NO){\cdot}CH_2{\cdot}N(NO){\cdot}OMe$] is distinctly yellow, and compounds of the type $RO{\cdot}NR{\cdot}NO$ have essentially the same type of spectrum as the nitrosamines $R_2N{\cdot}NO$. There is thus only slight contribution by the additional resonance forms made possible by the introduction of the extra oxygen atom. Somewhat surprisingly, a *N*-alkyl-*N*-nitrosohydroxylamine is colourless [see Table 1; also $Ph{\cdot}N(NO){\cdot}OH$ is a snow-white solid] and its absorption maximum is near to that for a nitramine. That this marked shift in absorption spectrum is not caused by isomerisation to the alkyl nitramine, $R{\cdot}NH{\cdot}NO_2$, in solution is shown (Carmack and Leavitt, *loc. cit.*) by the spectra of these compounds

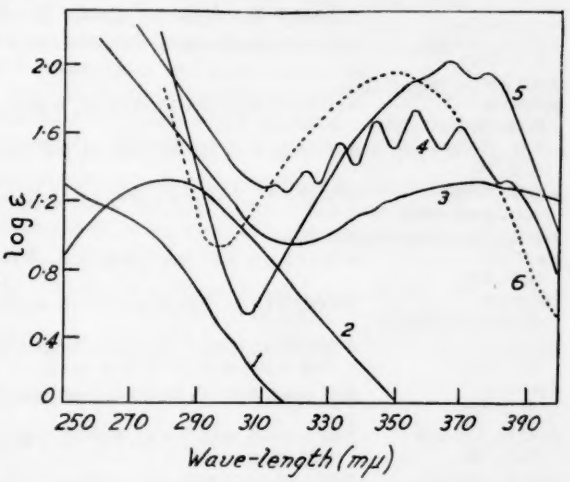
TABLE 1. *Ultra-violet spectra* (λ *in* mμ).

	Solvent	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{infl.}$	$\varepsilon_{infl.}$
Nitrosamines							
$Me_2N{\cdot}NO$	Light petroleum	374	105	369	90	—	—
		361	125	354	94	—	—
		351	98	301	3	—	—
		232	5,900	—	—	—	—
	EtOH [1]	346	100	294	11	—	—
		231	7,000	—	—	—	—
$Et_2N{\cdot}NO$	Light petroleum	378	90	374	85	—	—
		366	105	305	3	—	—
		233	6,500	—	—	355	80
	EtOH	350	90	297	8	—	—
		233	7,400	—	—	—	—
$Pr^n_2N{\cdot}NO$	Light petroleum	378	90	374	85	—	—
		366	110	307	5	—	—
		235	6,100	—	—	356	80
	EtOH	350	90	299	7	—	—
		233	7,000	—	—	—	—
$(n\text{-}C_5H_{11})_2N{\cdot}NO$	Light petroleum	378	90	374	85	—	—
		366	105	357	82	—	—
		356	85	311	12	—	—
		236	6,300	—	—	—	—
	EtOH	350	93	302	20	—	—
		235	7,400	—	—	—	—
$(n\text{-}C_6H_{13})_2N{\cdot}NO$	Light petroleum	378	95	374	85	—	—
		366	110	310	9	—	—
		235	6,200	—	—	355	85
	Ethanol	351	95	301	15	—	—
		235	7,450	—	—	—	—
N-Nitrosopiperidine	Light petroleum	377	65	372	60	—	—
		365	70	311	5	—	—
		238	4,200	—	—	355	55
	EtOH	351	95	302	12	—	—
		235	8,100	—	—	—	—
N-Nitro-*N'*-nitrosopiperazine	EtOH [2]	360	123	—	—	—	—
		242	12,900	—	—	—	—
Dinitrosopentamethylenetetramine	EtOH [2]	367·5	115	—	—	—	—
		230	10,750	—	—	—	—
1 : 3 : 5-Trinitroso-1 : 3 : 5-triaza-*cyclo*hexane	EtOH [2]	382	166	—	—	—	—
		370	174	—	—	—	—
		235	13,200	—	—	—	—
Nitrosohydroxylamines							
Dialkyl							
$MeO{\cdot}N(NO){\cdot}CH_2{\cdot}N(NO){\cdot}OMe$	EtOH [2]	380	100	—	—	—	—
		240	8,000	—	—	—	—
Monoalkyl							
$(HO{\cdot}CH_2)_3C{\cdot}N(NO){\cdot}OH$	H_2O [3]	229	6,000	—	—	—	—
$Me{\cdot}N(NO){\cdot}OH$	0·05N-NaOH [4]	244	8,000	—	—	286	250
$HO{\cdot}N(NO){\cdot}CH_2{\cdot}N(NO){\cdot}OH$ (" Traube compound ")	N-HCl [2]	231	12,600	—	—	—	—

TABLE 1. (*Continued.*)

	Solvent	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{infl.}$	$\varepsilon_{infl.}$
Nitrites							
BuO·NO	Light petroleum	384·5	33	381·5	31	—	—
		370	70	364	49	—	—
		356	87	349	46	—	—
		344	77	337·5	36	—	—
		333	56	326·5	27	—	—
		323	37	318	23	—	—
		314	27	310·5	24	—	—
		222	1,700	—	—	—	—
	EtOH	384	19	383	18·5	—	—
		370	38	364	30	—	—
		357	45	350	28·5	—	—
		344	40	338	22	—	—
		334	30	327	18	—	—
		323	21	318	15	—	—
		313	17	311	15	—	—
		218	1,050	—	—	—	—
Nitramines							
$Me_2N·NO_2$	Dioxan [2]	240	6,300	—	—	—	—
	H_2O [4]	238	8,000	—	—	—	—
$Cl·[CH_2·N(NO_2)]_3·Me$	Dioxan [2]	233	17,400	—	—	—	—
NN'-Dinitropiperazine	Dioxan [2]	250	11,000	—	—	—	—
$HN(NO_2)·CH_2·NH(NO_2)$	EtOH [2]	226	12,500	—	—	—	—

[1] Kortüm (*Z. physikal. Chem.*, 1941, **50**, *B*, 361; *Z. Elektrochem.*, 1941, **47**, 55) reports $\lambda_{max.}$ 333 mμ, ε 72·5, $\lambda_{min.}$ 286 mμ, ε 7·9, for an aqueous solution. [3] Jones and Thorn, *Canad. J. Res.*, 1949, **27**, *B*, 828. [3] Carmack and Leavitt, *J. Amer. Chem. Soc.*, 1949, **71**, 1221. [4] Kortüm and Finckh, *Z. physikal. Chem.*, 1940, **48**, *B*, 32.



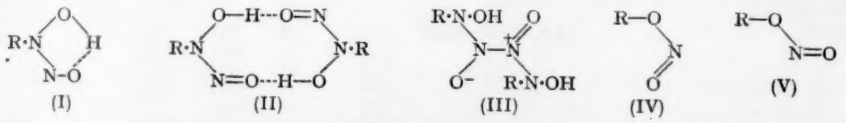
1, *Ethyl nitrate in light petroleum.*
2, 2-*Nitropropane in light petroleum.*
3, N-*Nitroso*-ON-*bistrifluoromethyl-hydroxylamine vapour.*
4, *Amyl nitrite in light petroleum.*
5, *Diethylnitrosamine in light petroleum.*
6, *Diethylnitrosamine in ethanol.*

[$(HO·CH_2)_3C·NH·NO_2$ in water, $\lambda_{max.}$ 235 mμ, ε 6190; cf. $Me·NH·NO_2$ in aqueous HCl, $\lambda_{max.}$ 232·5 mμ, ε 7200, $Bu·NH·NO_2$ in EtOH, $\lambda_{max.}$ 232·5 mμ, ε 7200 (Jones and Thorn, *loc. cit.*)] and by the shift in spectra when the solution is made alkaline. The monoalkyl-*N*-nitrosohydroxylamines are thus greatly different from the dialkyl compounds, even though resonance of the type $^{+}NR(OH){:}N{-}O^{-}$ can occur. In alkaline solution the difference might be ascribed to resonance in the anion:

$$\begin{array}{l} RN{-}O^{-} \\ \quad\| \\ \quad N{=}O \end{array} \longleftrightarrow \begin{array}{l} RN^{+}{=}O \\ \quad| \\ {-}N{-}O^{-} \end{array} \longleftrightarrow \begin{array}{l} RN^{+}{-}O^{-} \\ \quad| \\ \quad N{-}O^{-} \end{array}$$

but a more probable explanation, particularly for acid solution, is that intramolecular [(I), cf. Jones and Thorn, *loc. cit.*] or intermolecular (II) hydrogen bonding occurs, or that the compounds are dimeric (III) like the alkyl-*C*-nitroso-compounds, but do not revert to

the monomer in solution. In dialkylnitrosohydroxylamines hydrogen bonding of types (I) and (II) cannot occur.



The ultra-violet spectrum of *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine (see following paper) is shown in the Figure for comparison.

Relevant bands in the infra-red specta of *n*-butyl and *n*-amyl nitrite are shown in Table 2. These compounds are characterised by the three strong bands in the 6-μ region at 5·76, 6·07, and 6·23 μ, and by a strong, broad band near 12·5 μ. The spectrum is not substantially changed in the 6-μ region when chloroform is used as solvent; the band at 5·79 μ is then more intense than that at 6·12 μ, and the 6·23 μ band becomes an inflection. The bands near 6 μ are ascribed to the N=O stretching vibration (cf. monomeric *C*-nitroso-compounds which have N=O absorption in the 6·4—6·8-μ region; unpublished results), and the presence of two bands is ascribed to rotational isomers of the type IV and V.

The change in relative intensities of the N=O stretching vibration bands when the compound dissolves is consistent with a postulate of this type. Tarte (*J. Chem. Phys.*, 1952, **20**, 1570) has recently reported the doubling and temperature dependence of bands of methyl nitrite in the 6-μ region (5·95, 6·15 μ), and has postulated a C–H···O=N hydrogen bond to stabilise the *cis*-form.

TABLE 2. *Infra-red spectra* (5—10-μ *region*).

Nitrosyl chloride (C.S. 72)*	4·66, 4·70 (w. doublet), 5·50, 5·56 (v.v.s. doublet) (vapour)
Alkyl nitrites (liquid films).	
$Bu^nO·NO$ (C.S. 73)	5·75 (v.s.), 6·07 (v.v.s.), 6·23 (s), 6·83 (s), 7·27 (s), 7·72 (m), 7·84 (w), 7·95 (w), 8·10 (m)
n-$C_5H_{11}O·NO$ (C.S. 74)	5·76 (v.s.), 6·07 (v.v.s.), 6·23 (s), 6·81 (s), 7·30 (s), 7·83 (m), 8·07 (w)
n-$C_5H_{11}O·NO$ ($CHCl_3$ solution)	5·79 (v.v.s.), 6·12 (v.s.), 6·62 (w), 6·85 (s), 7·35 (m)
Dialkylnitrosamines (liquid films).	
$Me_2N·NO$ (C.S. 75)	5·75 (v.v.w.), 6·75 (v.w.), 6·92 (v.s.), 7·10 (s), 7·60 (v.s.), 7·76 (v.s.), 9·53 (v.s.)
$Me_2N·NO$ ($CHCl_3$ solution)	6·9 (s), 7·15 (s), 7·62 (v.s.), 7·71 (v.s.), 9·41 (s), 9·95 (v.s.)
$Et_2N·NO$ (C.S. 76)	5·73 (v.v.w.), 6·84, 6·94, 7·03 (s. triplet), 7·25 (v.s.), 7·37 (v.s.), 7·45 (s), 7·58 (v.s.) 8·09 (v.s.), 8·17 (v.s.), 9·35 (v.s.).
$Pr^n_2N·NO$ (C.S. 77)	6·87 (v.s.), 6·97 (s), 7·05 (m), 7·40 (v.s.), 7·65 (s), 7·83 (m), 8·35 (v.s.), 9·35 (v.s.)
$(n$-$C_5H_{11})_2N·NO$ (C.S. 78)	5·95 (v.v.w.), 6·85 (v.v.s.), 6·95 (s), 7·25 (s), 7·35 (v.s.), 7·60 (s), 7·95 (m), 8·47 (s), 9·22 (v.s.)
$(n$-$C_6H_{13})_2N·NO$ (C.S. 79)	5·95 (v.v.w.), 6·85 (v.v.s.), 6·95 (s), 7·25 (m), 7·36 (s), 7·6 (w), 7·75 (w), 8·05 (m), 8·6 (s), 9·18 (v.v.s.)
Nitrosopiperidine (C.S. 80)	5·63 (v.v.w.), 5·77 (v.v.w.), 6·82 (w), 6·92 (m), 7·00 (v.s.), 7·36 (v.v.s.), 7·80 (s), 7·95 (s), 8·49 (v.s.), 9·14 (v.s.)

m = medium, s = strong, v.s. = very strong, v.v.s. = extra strong, w = weak, s. triplet = strong triplet.

* Spectra thus denoted have been deposited with the Society. Photocopies, price 3*s.* 0*d.* each per spectrum, may be obtained on application, quoting the C.S. number, to the General Secretary.

The N–O vibration is assigned to the strong band at 12·5 μ (amyl nitrite) or 12·23, 12·7 (doublet, butyl nitrite), and the C–O vibration to the bands at 10·30 and 10·34 μ. The N–O vibration is thus at an abnormally long wave-length but the strength of the band leaves little doubt as to its assignment. The asymmetrical stretching vibration in the isomeric nitroalkanes is at 6·45 μ and the symmetrical stretching vibration is in the 7·25—

7·35-μ region (Haszeldine, *J.*, 1953, 2525). Aliphatic azoxy-compounds show asymmetrical and symmetrical stretching vibrations at 6·5—6·7 and 7·4—7·8 μ.

Relevant bands in the infra-red spectra of a series of dialkylnitrosamines are shown in Table 2. The most remarkable feature is the absence of a strong band in the usual N=O stretching vibration region. It is noteworthy that nitramines $R_2N{\cdot}NO_2$ and nitrates $RO{\cdot}NO_2$ show the NO_2 bands in the same region as $C{\cdot}NO_2$ compounds (6·1—6·5; 7·2—8·0 μ). Examination of the infra-red spectrum of dimethylnitrosamine dissolved in chloroform shows that it is substantially identical with that of the liquid nitrosamine (Table 2). Dimerisation to give $R_2N{\cdot}N(O^-){\cdot}N^+(:O){\cdot}NR_2$ (analogous to *C*-nitroso-dimers), although it would explain the shift of the N=O vibration, is thus improbable.

Two bands are plausible for the N=O vibration in nitrosamines: that at 7·1—7·4 μ, and that at 7·6—8·6 μ. The first of these bands is stronger than the band usually found at this position in alkyl compounds (*e.g.*, hydrocarbons), and particular support is given for its assignment by the fact that nitrosopiperidine, which contains CH_2 but no methyl groups, has a strong band at this point, as well as the usual CH_2 vibration at 6·9—7·0 μ. The assignment of the 7·6—8·6-μ band to the N=O vibration is supported by the strength of the band. Resonance of the type $R_2N{\cdot}N{=}O \longleftrightarrow R_2N^+{:}N{-}O^-$ would cause a shift towards the N–O vibration at longer wave-length. The N–O vibration can clearly be assigned to the very strong band in the 9·15—9·55-μ region. Three strong bands thus characterise dialkylnitrosamines: the N=O vibration, a band *ca.* 8 μ, and a band (N·O) *ca.* 9·5 μ [R in $R_2N{\cdot}NO$: Me, 7·10; 7·60, 7·76 (doublet); 9·53. Et, 7·37; 8·09, 8·17 (doublet); 9·35. Pr^n, 7·40; 8·35; 9·35. *n*-C_5H_{11}, 7·35; 8·47; 9·22. *n*-C_6H_{13}, 7·36; 8·60; 9·18. Nitrosopiperidine, 7·35; 8·49; 9·14 μ].

Ultra-violet and infra-red spectra thus enable nitrosamines and nitrites to be distinguished from other compounds containing nitrogen and oxygen. Furthermore, since the change in ultra-violet absorption and in the characteristic infra-red vibrations of nitro-, nitroso-, azo-, and azoxy-compounds is not great when fluorine is substituted into the molecule (Haszeldine, *J.*, 1953, 2525, and unpublished results), the correlation of spectra with constitution determined for compounds which do not contain fluorine can be used diagnostically for fluorine compounds, as is shown in the following paper.

Experimental.—A Unicam Spectrophotometer and a Perkin-Elmer Model 21 Double Beam Spectrophotometer were used; the latter had rock-salt optics. Solvents were dried, and moisture was carefully excluded. Maxima in the range 210—400 mμ were measured to 0·25 mμ and in the range 400—800 mμ to 0·5 mμ.

The authors are indebted to Dr. A. I. Vogel for a gift of dipentyl- and dihexyl-nitrosamine and of nitrosopiperidine, and to Mr. F. E. G. Smith for the preparation of dimethyl-, diethyl-, and dipropyl-nitrosamine. Other compounds were purified by distillation before spectroscopic examination.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 5th*, 1953.]

Addition of Free Radicals to Unsaturated Systems. Part VI. Free-radical Addition to the Nitroso-group.*

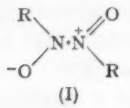
By J. JANDER and R. N. HASZELDINE.

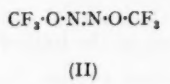
[Reprint Order No. 4557.]

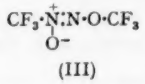
Trifluoronitrosomethane is rapidly and quantitatively converted into the brownish-red *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine on exposure to ultra-violet light; this is interpreted as involving a free-radical addition to the N=O bond, with the radical $CF_3\cdot\dot{N}\cdot O\cdot CF_3$ as intermediate. Other possibilities [particularly $(CF_3)_2N\cdot O\cdot NO$] for the product are considered and discarded. Spectroscopic evidence is presented.

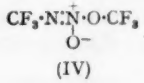
TRIFLUORONITROSOMETHANE (Haszeldine, *J.*, **1953**, 2075; Haszeldine and Jander, *J.*, **1953**, 4172) is a deep blue monomeric gas which condenses to a deep blue liquid. Its Trouton constant (21·9) indicates that the liquid is not associated. As pointed out earlier, the perfluoroalkylnitroso-compounds differ from other nitroso-compounds, since they cannot isomerise in the same way as their unsubstituted analogues (>CH·NO ⟶ >C:N·OH) and they do not dimerise, even at −150°, to give dimers of the type (I).

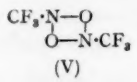
Trifluoronitrosomethane is completely stable in the dark, even after several years, but on exposure to light, and particularly to ultra-violet light, the blue gas (b. p. −87°) changes almost quantitatively into a brownish-red gas of much higher boiling point (10°). This product is stable at moderate temperatures, and is unaffected by water or hydrochloric acid, but is decomposed by aqueous sodium hydroxide; it has a normal Trouton constant (21·5). The compound, $C_2O_2N_2F_6$, is not the dimer of the type (I; R = CF_3), since it is deeply coloured; furthermore the blue trifluoronitrosomethane is not liberated when the

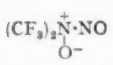

(I)

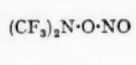

(II)

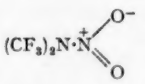

(III)

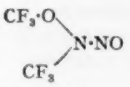

(IV)


(V)


(VI)


(VII)


(VIII)


(IX)

compound is heated alone or is dissolved in an organic solvent. All known dimers of nitroso-compounds are colourless (even when R = Ph), and revert, at least in part, to the coloured monomer when heated or dissolved. Possible constitutions are (II)—(IX), and that the compound is *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine (IX) is shown by spectroscopic evidence.

Absorption of $C_2O_2N_2F_6$.

Ultra-violet spectrum.

Vapour	$\lambda_{max.}$ 374 mμ	$\varepsilon_{max.}$ 20	$\lambda_{min.}$ 320 mμ	$\varepsilon_{min.}$ 8·5
Slight inflections	398 mμ, ε 16·6	390 mμ, ε 18·4	378 mμ, ε 19·5	368 mμ, ε 19·5
	356 mμ, ε 18·0	349 mμ, ε 16·0	341 mμ, ε 12·5	

Infra-red spectrum of vapour in 5—10-μ region (C.S. 81 *) 5·47, 5·55 (v.s. doublet), 5·65 (w), 6·14 (w), 6·65 (v.w.), 7·62 (v.s.), 7·85 (v.s.), 7·98 (m), 8·19 (v.s.), 8·83 (w), 9·35 (v.s.), 10·20 (v.s.), 11·75 (v.s.), 12·98 (v.s.), 13·98 (v.s.).

* Spectra thus denoted have been deposited with the Society. Photocopies may be obtained, price 3*s.* 0*d.* each per spectrum, on application, stating the C.S. number, to the General Secretary.

Its ultra-violet spectrum (Table; see also Fig. in preceding paper) shows a maximum at 374 mμ with fine structure from 340 to 400 mμ. The following possible constitutions can thus be discarded on the basis of chemical properties and colour: (II), since hypo-

* Parts I—V, *J.*, 1952, 2504; 1953, 1199, 1592, 3559, 3565.

nitrites and azo-ethers are colourless and unstable ($HO\cdot N{:}N\cdot OH$ in 0·1N-HCl, inflection 244 mμ, ε 80; in 0·1N-NaOH, $\lambda_{max.}$ 244 mμ, ε 3550, inflection 294 mμ, ε 25; Körtum and Finckh, *Z. physikal. Chem.*, 1940, **48**, *B*, 32. $Ph\cdot N{:}N\cdot OMe$ is colourless; Bamberger, *Ber.*, 1895, **28**, 225); (III) and (VI), since they would be colourless like an azoxy-compound ($MeN{:}\overset{+}{N}Me\cdot O^-$ in EtOH: $\lambda_{max.}$ 217 mμ, ε 7250; inflection 274 mμ, ε 45; Langley, Lythgoe, and Rayner, *J.*, 1952, 4191); (IV), since *iso*nitramines are colourless [*e.g.*, *ON*-dimethyl-*iso*nitramine, $Me\cdot N{:}\overset{+}{N}(OMe)\cdot O^-$; Franchimont and Umbgrove, *Rec. Trav. chim.*, 1896, **15**, 213]; (V), since it would be colourless; and (VIII), since nitramines are colourless (see preceding paper). Both (VII) and (IX) are possible on grounds of colour (see preceding paper). Compounds analogous to (VII) are unknown, and would be expected to be unstable, and to have an ultra-violet spectrum like that of a nitrite, since the amine nitrogen can contribute little to resonance:

$$(CF_3)_2N\cdot O\cdot N{=}O \longleftrightarrow (CF_3)_2N{-}\overset{+}{O}{=}N{-}O^-$$

cf.
$$(CF_3O)(CF_3)N\cdot N{=}O \longleftrightarrow (CF_3O)(CF_3)\overset{+}{N}{=}N{-}O^-$$

Unlike nitrites and nitrosamines, $C_2O_2N_2F_6$ does not show a high-intensity band in the near ultra-violet, although the end-absorption is strong (ε 540 at 220 mμ, 900 at 210 mμ). Its absorption maximum lies very close to that of the β-methyl ester of Traube's compound or to that of a nitrosamine (see preceding paper), and it is noteworthy that *ON*-dimethyl-*N*-nitrosohydroxylamine is described as a stable yellow oil (Boese, Jones, and Major, *J. Amer. Chem. Soc.*, 1931, **53**, 3530). This suggests that (IX) is much more probable than (VII).

The infra-red spectrum of the compound $C_2O_2N_2F_6$ is also in favour of (IX). It is known that there is only a slight shift (<0·5 μ) in the characteristic vibrations of nitro-, nitroso-, and azoxy-compounds, when fluorine is substituted on the α-carbon atom or atoms (Haszeldine, *J.*, 1953, 2525; Haszeldine and Jander, in the press). The spectrum of $C_2O_2N_2F_6$ (Table) shows the carbon–fluorine vibration at 8·19 and possibly 7·85 μ; there are no strong bands between 5·7 and 7·5 μ, the region shown to be characteristic of the nitrite group. The strong bands at 7·62 (N=O) and 9·35 μ (N—O) fall, however, into the region shown in the preceding paper to be characteristic of nitrosamines, *i.e.*, are in accord with constitution (IX). If the compound had constitution (VII) then the doublet at 5·47, 5·55 μ, and the 10·20, 11·75, or 12·98 μ bands would have to be assigned to the –O·NO system, and the shifts from the usual nitrite vibrations would be abnormally large; on the basis of (IX), the 5·5-μ doublet is assigned to a combination frequency, and the fact that it is at a similar wave-length to the N:O vibration in nitrosyl chloride (Table 2, preceding paper) is probably fortuitous.

The spectroscopic evidence is thus in favour of (IX), but full confirmation of the above argument must await a detailed chemical investigation in a field where there are at present no established reference compounds.

If it is assumed that on irradiation trifluoronitrosomethane decomposes into a trifluoromethyl radical and nitric oxide, then the following mechanism for the formation of *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine can be suggested:

$$CF_3\cdot NO \xrightarrow{h\nu} CF_3\cdot + NO$$

$$CF_3\cdot + CF_3\cdot N{=}O \longrightarrow CF_3\cdot\dot{N}\cdot O\cdot CF_3$$

$$CF_3\cdot\dot{N}\cdot O\cdot CF_3 + NO \longrightarrow CF_3\cdot N(NO)\cdot O\cdot CF_3$$

or
$$CF_3\cdot\dot{N}\cdot O\cdot CF_3 + CF_3\cdot NO \longrightarrow CF_3\cdot N(NO)\cdot O\cdot CF_3 + CF_3\cdot \longrightarrow \text{etc.}$$

The addition of a trifluoromethyl radical to a carbon–carbon double bond is well established (see, *e.g.*, Parts I—V), but free-radical addition to a nitrogen–oxygen double bond has not been noted earlier. The CF_3 radical initiates the reaction by attack on the more negative atom, to give the relatively more stable radical [cf. (VII) which could be formed by a similar mechanism involving attack on the nitrogen atom to give $(CF_3)_2N\cdot\dot{O}$ as inter-

mediate]. The chain reaction similar to that proposed for the reaction of trifluoroiodomethane with olefins (Part I) explains why compounds of the type $(CF_3)_2N{\cdot}O{\cdot}CF_3$ or $CF_3{\cdot}N(NO){\cdot}O{\cdot}NO$ are not formed. Free-radical attack on the oxygen atom of a C:O group in a quinone has been established recently (Waters *et al.*, *J.*, 1950, 1764; 1952, 4666). Support for the above radical mechanism is given by the isolation of hexafluoroethane as by-product.

Further studies on free-radical addition reactions with nitroso-compounds will be described in a later paper.

Experimental

Trifluoronitrosomethane, prepared from trifluoroiodomethane or from silver trifluoroacetate by the methods described earlier (Haszeldine, *J.*, 1953, 2075; Haszeldine and Jander, *J.*, 1953, 4172), was purified by distillation *in vacuo*.

Photochemical Reaction of Trifluoronitrosomethane.—Trifluoronitrosomethane (0·1 g.), sealed in a 0·5-ml. Pyrex tube and left in the dark for 4—5 years, was recovered unchanged.

The nitroso-compound (0·95 g.) was kept in a previously evacuated 3-l. soda-glass bulb sealed to an 80-ml. trap. The bulb was painted black, but the trap was left exposed to diffuse daylight for 2 weeks. The condensed nitroso-compound was then green. Fractionation *in vacuo* gave *N-nitroso*-ON-*bistrifluoromethylhydroxylamine* (0·19 g., 20% conversion, 95% yield), a reddish-brown liquid, b. p. 10° (Found: C, 12·0; N, 14·2%; *M*, 198. $C_2O_2N_2F_6$ requires C, 12·1; N, 14·1%; *M*, 198), and unchanged trifluoronitrosomethane.

In another experiment trifluoronitrosomethane (0·20 g.) was kept in a previously-evacuated 3-l. bulb and exposed to full daylight (and sunlight) for 36 hr. The condensed green liquid was fractionated to give *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine (0·15 g., 75% conversion). The unchanged starting material was returned to the bulb and left until the colour of trifluoronitrosomethane had disappeared (*ca.* 7 weeks). Distillation and spectroscopic analysis revealed *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine (0·194 g., 97% total), hexafluoroethane (4 mg., 2%), silicon tetrafluoride (1 mg.), trifluoronitromethane (*ca.* 1 mg.), and trifluoronitrosomethane (*ca.* 1 mg.).

An almost quantitative yield of *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine was obtained by exposure of trifluoronitrosomethane (0·05 g.) in a 5-ml. Pyrex tube to ultra-violet light. There was *ca.* 10% reaction after 1 hr. and complete reaction after 40 hr.

Properties of N-*Nitroso*-ON-*bistrifluoromethylhydroxylamine.*—The vapour pressure, measured between −1° and +10°, is given by $\log_{10} P$ (mm.) = 7·576 − 1329·1/T, where T is the temperature (K). The b. p. is calculated as 9·9°, the latent heat of vaporisation as 6080 cal./mole, and Trouton's constant as 21·5.

Reactions of N-*Nitroso*-ON-*bistrifluoromethylhydroxylamine.*—(a) *On being heated.* The compound (0·050 g.), heated at 100° for 1 hr. in a 5-ml. silica tube, became slightly paler. After 3 days a small amount of a non-condensable gas had been formed, and distillation of the residual material gave a fraction (0·045 g.) shown by infra-red examination to contain unchanged starting material and an unidentified compound characterised by strong bands at 6·0 and 6·65 μ; the mixture (*M*, 183) could not be separated by distillation *in vacuo*. Trifluoronitrosomethane was not a reaction product. Prolonged heating (4 weeks) caused attack on the silica tube.

(b) *With aqueous reagents.* There was no reaction when *N*-nitroso-*ON*-bistrifluoromethylhydroxylamine was kept with water or 20% hydrochloric acid at room temperature, or at 50° for 6 hr.

Decomposition was complete after 24 hr. in a sealed tube with 10% sodium hydroxide at room temperature. A trace of hexafluoroethane was detected in the otherwise unidentified small amount of gaseous product, and qualitative tests on the aqueous solution for fluoride and nitrite were positive.

One of us (J. J.) thanks Professor H. J. Emeléus for his personal interest and The British Council for a British Council Scholarship for Germany during the tenure of which this work was carried out.

University Chemical Laboratory, Cambridge. [*Received, August 5th*, 1953.]

Epimeric Alcohols of the cyclo*Hexane Series. Part X.** (±)-trans-3-*Methyl*cyclo*hexanecarboxylic Acid and* (±)-trans-3-*Methyl*cyclo*hexylamine.*

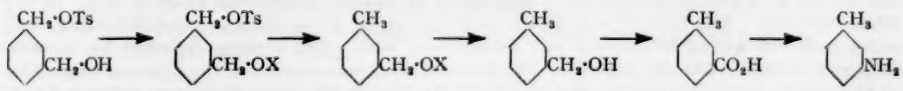
By F. R. Hewgill, P. R. Jefferies, and A. Killen Macbeth.

[Reprint Order No. 4698.]

(±)-*trans*-3-Methyl*cyclo*hexanecarboxylic acid and (±)-*trans*-3-methyl*cyclo*hexylamine have been prepared by a series of stereochemically specific steps.

Frahn, Macbeth, and Shannon (unpublished work) prepared mixtures of the (±)-3-methyl*cyclo*hexylamines by hydrogenation with Raney nickel of aceto-*m*-toluidide under pressure, followed by hydrolysis, and by similar hydrogenation of *m*-toluidine. From the products a (±)-3-methyl*cyclo*hexylamine was obtained to which the *trans*-configuration would have been assigned on the basis of the Auwers–Skita rule, but the substance was shown to be the *cis*-amine (Macbeth, Aust. and N.Z. Assoc. for Advancement of Science, Sydney, August, 1952) by application of the stereochemically specific Schmidt reaction (Campbell and Kenyon, *J.*, 1946, 25; Dauben and Hoerger, *J. Amer. Chem. Soc.*, 1951, **73**, 1504) to (±)-*cis*-3-methyl*cyclo*hexanecarboxylic acid; the configuration of the acid follows from its relation to the corresponding methanol unequivocally synthesised by Owen and later described by Haggis and Owen (*J.*, 1953, 408). Noyce and Nagle (*J. Amer. Chem. Soc.*, 1953, **75**, 127) independently established the *cis*-configuration of the amine, and a detailed account of our work on the *trans*-amine only is now reported.

The literature on the preparation of the 3-methyl*cyclo*hexylamines need not be reviewed as only in a few cases were attempts made to separate the mixtures of epimers formed. In order to obtain stereochemically pure samples of the *trans*-acid and amine, and to provide a chemical proof of their configuration, we have used a synthesis which proceeds by stereochemically specific steps from *trans*-hexahydro*iso*phthalic acid, whose configuration has been rigorously established (Böeseken and Peek, *Rec. Trav. chim.*, 1925, **44**, 845). This acid was obtained by platinum-catalysed hydrogenation of *iso*phthalic acid under atmospheric conditions, followed by separation of the epimers through the calcium salts. The purity of the acetic acid employed as the solvent was found to be most critical in this hydrogenation. Reduction of the dimethyl ester with lithium aluminium hydride has been shown by Haggis and Owen (*J.*, 1953, 389) to proceed with retention of the configuration, and the diol so obtained was converted into the monotoluene-*p*-sulphonate (I) by the method described by these authors. The melting point and crystalline form of the *p*-nitrobenzoate of (I) differed from those of the sample prepared by Haggis and Owen.



(I) (II) (III) (IV) (V) (VI)

(Ts = *p*-$C_6H_4Me\cdot SO_2$; X = tetrahydro-2-pyranyl.)

Protection of the alcoholic group of (I) by formation of the tetrahydropyranyl ether (II) and reduction of the toluene-*p*-sulphonyl group with lithium aluminium hydride (Karrer, Asmis, Soreen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022) gave (III), converted into *trans*-3-methyl*cyclo*hexylmethanol (IV) by acid hydrolysis (compare Goering and Serres, *J. Amer. Chem. Soc.*, 1952, **74**, 5908). This procedure gave a much better yield of (IV) than was obtained by Haggis and Owen (*J.*, 1953, 408). Oxidation of (IV) to *trans*-3-methyl*cyclo*hexanecarboxylic acid (V) was accomplished smoothly with the chromic acid reagent described by Curtis, Heilbron, Jones, and Woods (*J.*, 1953, 457). Conversion of the acid (V) into *trans*-3-methyl*cyclo*hexylamine was carried out by the

* Part IX, *J.*, 1953, 1364.

stereochemically specific Schmidt reaction. The presence of a lower-boiling fraction in the crude amine might be attributed to the formation of methyl*cyclo*hexenes, since the amino-group might occupy a polar position and groups in polar positions are favourably situated for bimolecular elimination.

It will be observed that the physical constants of the *trans*-epimers obtained are without exception higher than those of the corresponding *cis*-compounds, although in one or two cases allowances for temperature differences must be made. In addition, the melting points of all the (±)-*trans*-epimers are lower than those of the corresponding (±)-*cis*-derivatives. As well as providing further justification for the reversal of the Auwers–Skita rule for the 1 : 3-disubstituted *cyclo*hexanes (von Auwers and Schmelzer, *Chem. Zentr.*, 1927, II, 1562) these results are in accord with the recent work of Pitzer *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 977, 2488), Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), and Hassel and Furberg (*ibid.*, 1950, **4**, 597) indicating that of pairs of geometrical isomers the one possessing the greater steric hindrance will also have higher physical constants, *i.e.*, the *cis*-1 : 2-, the *trans*-1 : 3-, and the *cis*-1 : 4-disubstituted *cyclo*hexanes.

Experimental

Dimethyl trans-*Hexahydroiso**phthalate*.—*iso*Phthalic acid, twice recrystallised from 95% ethanol, was quantitatively hydrogenated in suspension in carefully fractionated glacial acetic acid, over Adams platinum oxide at room temperature and atmospheric pressure. The *cis*-+*trans*-hexahydro*iso*phthalic acids so obtained (m. p. 117—126°) were separated through their calcium salts, and the *cis*-acid partially isomerised (Skita and Rössler, *Ber.*, 1939, **72**, 265). From 60 g. of mixed isomers, several repetitions of this isomerisation and separation afforded 28 g. of *trans*-acid, which was again purified through the calcium salt and twice recrystallised from water.

The *trans*-acid (m. p. 150—151°) was esterified with methyl iodide through its silver salt (Skita and Rössler, *loc. cit.*).

trans-1 : 3-*Bishydroxymethyl*cyclo*hexane*.—The *trans*-dimethyl ester was reduced with lithium aluminium hydride in high yield by a method essentially similar to that of Haggis and Owen (*loc. cit.*). The ditoluene-*p*-sulphonate of the diol had m. p. 91—92°, and the di-*p*-nitrobenzoate, m. p. 122—123°. Haggis and Owen give 86—87° and 122—123° respectively.

The monotoluene-*p*-sulphonate of the diol was prepared under conditions identical with those described by Haggis and Owen (*loc. cit.*) in 57% yield, and the p-*nitrobenzoate* thereof crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 85° (Found : C, 59·4; H, 5·7; N, 3·3. $C_{22}H_{25}O_7NS$ requires C, 59·1; H, 5·6; N, 3·1%). Haggis and Owen report this to be a microcrystalline powder, m. p. 97—98°.

trans-3-*Methyl*cyclo*hexylmethanol*.—A solution of the monotoluene-*p*-sulphonate (13·5 g.) in freshly purified dihydropyran (25 ml.) was shaken for 20 min. with three drops of concentrated hydrochloric acid and then set aside for 15 hr. The excess of dihydropyran was removed *in vacuo* and the residual sweet-smelling tetrahydropyranyl ether (17·3 g.) in dry ether (50 ml.) was added to a mechanically stirred suspension of lithium aluminium hydride (6 g.) in dry ether (300 ml.). The mixture was boiled under reflux for 30 hr. with occasional stirring, and, when cool, the excess of hydride was decomposed with ethyl acetate, followed by aqueous sodium hydroxide (200 ml. of 10%). The ethereal layer was separated, the aqueous suspension of aluminium hydroxide was filtered, and both the filtrate and precipitate were extracted with ether. Evaporation of the combined ethereal extracts gave a residue (11·5 g.) which was boiled in methanol (200 ml.) under reflux for 2 hr. after addition of 5N-hydrochloric acid (40 ml.). The resultant liquid was diluted with water, and the methanol removed through a short column. Extraction of the aqueous residue with light petroleum (b. p. 60—70°) and evaporation of the dried extract gave an oil, which was fractionally distilled at 15 mm., yielding materials (*a*) (2·4 g.), b. p. 94—96°, n_D^{22} 1·4628, d_4^{22} 0·9252, $[R_L]_D$ 38·17 (calc. 38·47), and (*b*) (1·0 g.), b. p. 96—130° (residue 2·5 g.).

A portion of fraction (*a*) was converted into *trans*-3-methyl*cyclo*hexylmethyl 3 : 5-dinitrobenzoate, m. p. 78—79°. Haggis and Owen (*loc. cit.*) give m. p. 77—78°. A further quantity of this ester was obtained by esterification of fraction (*b*). Chromatography of the crude product on acid-washed alumina and elution with light petroleum (b. p. 50—70°)–benzene (8 : 1) gave the ester (1·0 g.), m. p. and mixed m. p. 78—79°.

trans-3-*Methyl*cyclo*hexanecarboxylic Acid*.—*trans*-3-Methyl*cyclo*hexylmethanol (2·1 g.) in

pure acetone (20 ml.) was titrated at 20° with an acid solution of chromium trioxide (8N with respect to oxygen). To produce a persistent orange-brown colour 8·4 ml. of the reagent were required (theory, 8·2 ml.). The mixture was diluted with water, and the crude acid extracted with ether. After removal of the solvent from the dried ($MgSO_4$) extract, the residue was distilled, yielding the *acid* (1·5 g.), b. p. 92°/1·3 mm., n_D^{20} 1·4618, d_4^{20} 1·0051, $[R_L]_D$ 38·58 (calc. 38·48) (Found : C, 68·1; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 10·0%). It gave an *anilide*, plates, m. p. 123° [from light petroleum (b. p. 60—70°)], depressed to 107—113° on admixture with the anilide derived from the *cis*-acid (Found : C, 77·6; H, 8·7. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%), and a p-*bromophenacyl* ester, plates, m. p. 56—57° (from aqueous methanol) (Found : C, 56·6; H, 5·8; Br, 23·7. $C_{16}H_{19}O_3Br$ requires C, 56·7; H, 5·7; Br, 23·6%).

trans-3-*Methyl*cyclo*hexylamine*.—Powdered sodium azide (0·75 g.) was added in portions during 30 min. to a well-stirred solution of *trans*-3-methyl*cyclo*hexanecarboxylic acid (1·1 g.) in chloroform (25 ml.) and concentrated sulphuric acid (15 ml.) kept at 40°. The temperature was raised to 50° and stirring continued for a further 30 min. When cool, the mixture was poured on crushed ice and separated. Evaporation of the chloroform gave a negligible residue. The aqueous layer was made alkaline with 10% sodium hydroxide solution, the amine extracted with ether, and the extract washed with water and dried (KOH). The ether was removed through a fractionating column, and the crude residue (0·7 g.) distilled. Redistillation of the higher-boiling fraction gave *trans*-3-methyl*cyclo*hexylamine (0·3 g.), b. p. 150·5—151°/767 mm., n_D^{16} 1·4610, d_4^{15} 0·8760, $[R_L]_D$ 35·46 (calc. 35·75). It gave a p-*nitrobenzoyl* derivative, plates, m. p. 104—105°, from aqueous methanol (Found : C, 64·3; H, 6·8; N, 10·8. $C_{14}H_{18}O_3N_2$ requires C, 64·2; H, 6·9; N, 10·7%). The carbonate (needles) had m. p. 81—83° (sealed tube).

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

JOHNSON CHEMICAL LABORATORIES,
THE UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, October 5th*, 1953.]

---

p-*Menthane*-2 : 3-*diols*. *Part III*.* *Reductions of Diosphenol with Aluminium* iso*Propoxide and with Lithium Aluminium Hydride*.

By A. KILLEN MACBETH and W. G. P. ROBERTSON.

[Reprint Order No. 4534.]

The diol formed on reduction of diosphenol with aluminium *iso*propoxide is mainly (±)-*trans*-2-hydroxy*neo*menthol. Appreciable amounts of (±)-*cis*-2-hydroxy*iso*menthol and, probably, (±)-*cis*-2-hydroxy*neo*menthol are also produced, and the presence of (±)-*trans*-2-hydroxy*iso*menthol is established. Lithium aluminium hydride reduction under all conditions tried yields considerable amounts of partially reduced compounds and the yield of glycols is low. The di-*p*-nitrobenzoates of (±)-*trans*-2-hydroxy*neo*menthol and of, probably, (±)-*cis*-2-hydroxy*neo*menthol have been isolated.

The reductions with these reagents are of stereochemical interest but are of limited preparative value.

IN the reduction of a number of substituted *cyclo*hexanones by aluminium *iso*propoxide (Jackman, Macbeth, and Mills, *J.*, 1949, 2641) and by lithium aluminium hydride (Noyce and Denney, *J. Amer. Chem. Soc.*, 1950, **72**, 5743; Macbeth and Shannon, *J.*, 1952, 2852) the former reagent generally gave a larger proportion of the *cis*-isomer. As the differences are doubtless due to the smaller steric requirements of the reducing step of the lithium aluminium hydride reaction (Trevoy and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675) a comparison of the behaviour of the two reagents with diosphenol appeared to be of stereochemical interest.

Reduction of diosphenol by aluminium *iso*propoxide was slow and the rather poor yield of diol was not improved by a modified procedure (Macbeth and Mills, *J.*, 1949, 2646). Fractional distillation of the crude product obtained by use of 2·5 mols. of aluminium *iso*propoxide for 13 hr. yielded a glycol fraction of some 23%, with a fore-run of unchanged

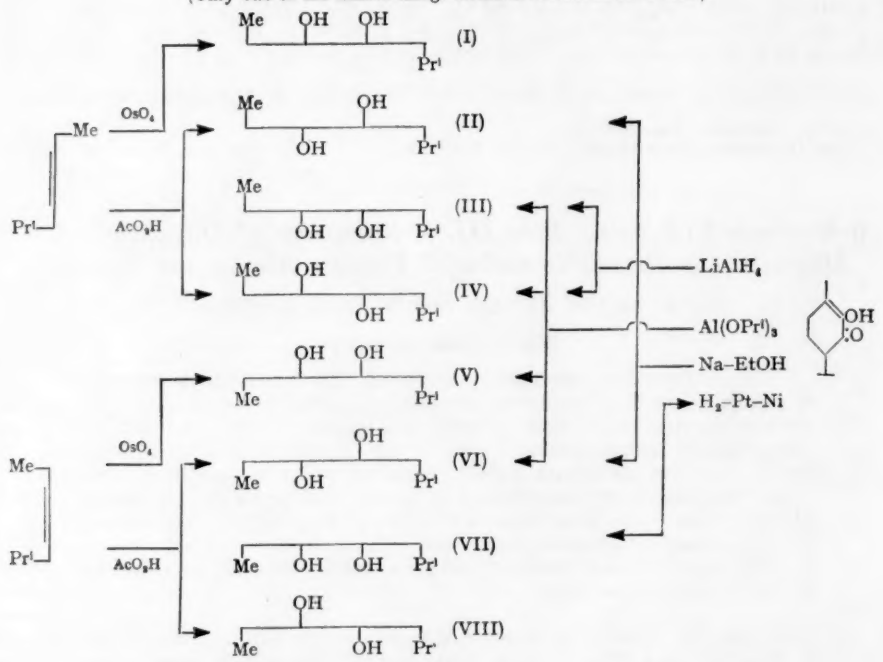
* Part II, *J.*, 1953, 3512.

diosphenol apparently free from products of partial reduction; the yield of mixed glycols was increased to 43% by use of 5 mols. of the *iso*propoxide for 40 hr. Crystallisation of the whole fraction from light petroleum gave (±)-*trans*-2-hydroxy*neo*menthol (IV*a*). Fractional crystallisation of the di-*p*-nitrobenzoates of the material from the mother-liquors gave the known esters (V*b*) and (VI*b*) and a new ester, m. p. 165—166°. The previously unknown glycol (V*a*) was obtained by hydrolysis of (V*b*), and the new ester gave a new glycol. Seven of the eight (±)-*p*-menthane-2 : 3-diols being previously known, the new one is presumably the eighth, *cis*-2-hydroxy*neo*menthol (III).

The formation of (±)-*trans*-2-hydroxy*neo*menthol as the main product of the reduction of diosphenol by aluminium *iso*propoxide supports the configuration assigned to it (Part II), since consideration of the mechanism of the reduction of carbonyl compounds by aluminium alkoxides (Jackman and Mills, *Nature*, **1949**, **164**, 789; Doering and Young, *J. Amer. Chem. Soc.*, **1950**, **72**, 630; Jackman, Mills, and Shannon, *ibid.*, **1950**, **72**, 4814; Jackman and Macbeth, *J.*, **1952**, 3252) suggests the preferential formation of the more sterically hindered of a pair of epimeric alcohols.

The isomeric (±)-*2-hydroxymenthols.*

(Only one of the mirror-image forms is shown in each case.)



(*a*) = Glycol. (*b*) = Di-*p*-nitrobenzoate. (*c*) Bis-3 : 5-dinitrobenzoate.

Series	(*a*)	(*b*)	(*c*)	Series	(*a*)	(*b*)	(*c*)
cis (I)	—	163°	—	*cis-iso* (V)	70·5—71°	138°	143°
trans (II)	91°	118	218°	*trans-iso* (VI)	77	166	122
cis-neo (III) ...	52	165—166	—	*cis-neoiso* (VII) ...	76	147—148	82—83
trans-neo (IV) ...	79	168	173	*trans-neoiso* (VIII)	69	152—153	65

Reduction of 1 : 2-diketones to glycols by lithium aluminium hydride appears to have been achieved in very few cases—it gives predominantly *cis*-camphane-2 : 3-diol from 2 : 3-camphorquinone (Trevoy and Brown, *loc. cit.*), and the *trans*-glycols from 1 : 2-naphthaquinone, 1 : 2-anthraquinone, and 9 : 10-phenanthraquinone (Booth, Boyland, and Turner, *J.*, 1950, 1188). Reduction of diosphenol by 2, 4, or 10 equivalents of lithium

aluminium anhydride in boiling ether for 3 hr. gave 30%, 40%, and 46% yields respectively of crude glycols. There were large amounts of lower-boiling products; although these might contain hydroxy-ketones, no *p*-nitrobenzoate, semicarbazone, or 2 : 4-dinitrophenylhydrazone could be crystallised; this fraction slowly deposited prisms, m. p. 159—163°, which were not further examined but may be the substance, m. p. 159°, obtained by Shimoyama (*Arch. Pharm.*, 1888, **26**, 403) by the sodium amalgam reduction of diosphenol (Simonsen, "The Terpenes," MacMillan, 1947, Vol. I, p. 419, suggested that this is a pinacone, $C_{20}H_{34}O_4$). Tedious fractional crystallisation of the glycol di-*p*-nitrobenzoates gave (IV*b*) and (III*b*), but (IV*a*) did not crystallise directly from the mixed glycols in this case.

The complete work on the diols and the melting points of the characteristic esters are shown in the chart and Table.

Experimental

Reduction of Diosphenol with Aluminium iso*Propoxide*.—(*a*) To a boiling stock M-solution of aluminium *iso*propoxide in *iso*propanol (50 ml.) were added dry *iso*propanol (50 ml.), and then, dropwise during 8 hr., a solution of diosphenol (10 g.) in *iso*propanol (100 ml.). The distillate was continuously fractionated through a bead-column 75 cm. in length, and after the addition of diosphenol the fractionation was continued until the distillate no longer gave a test for acetone (13 hr.). A further portion of *iso*propanol (25 ml.) was removed by more rapid fractionation. The residue was diluted with water (150 ml.) and extracted with benzene (50 + 25 ml.). The extract was washed with 12N-sulphuric acid (30 ml.), 2N-sodium hydroxide (2 × 25 ml.), and water (25 ml.), and dried ($MgSO_4$). After removal of the solvent, distillation of the residue gave fractions, (i) colourless crystals (3 g.), b. p. 80—95°/4 mm., and (ii) a viscid colourless oil (2·3 g.), b. p. 110—120°/4 mm. Acidification of the alkaline washings precipitated diosphenol (1 g.). Crystallisation of fraction (i) from light petroleum (b. p. 40—60°) gave diosphenol (2 g.), m. p. 82°. Crystallisation of fraction (ii) from light petroleum (b. p. 40—60°) gave (±)-*trans*-2-hydroxy*neo*menthol (0·2 g.), m. p. 79° [di-*p*-nitrobenzoate (pale yellow plates from ethanol), m. p. 168°]. Both the glycol and its ester showed no depression of m. p. on admixture with authentic specimens (Part II).

(*b*) Diosphenol (15 g.) in dry *iso*propanol (150 ml.) was added to a boiling M-solution of aluminium *iso*propoxide in *iso*propanol (150 ml.) during 7 hr. The reduction was continued under reflux in the usual way, a column (100 cm.) packed with single-turn glass helices and a high reflux ratio being used for 40 hr.; 200 ml. of distillate were collected. The residue was worked up in the usual way. Fractionation through a small column of glass helices gave (*a*) crystalline diosphenol (4 g.), b. p. 85—90°/4 mm., and (*b*) a colourless viscid oil (6·5 g.), b. p. 112—118°/4 mm. A further 2 g. of diosphenol were recovered from the alkaline washings. Crystallisation of fraction (*b*) from light petroleum (10 ml.) (b. p. 40—60°) gave (±)-*trans*-2-hydroxy*neo*menthol (2·2 g.) as fine white needles, m. p. 76—79° (recrystallised, m. p. 79°).

The viscous oil (7 g.) recovered from the petroleum mother-liquors was fractionally distilled through a small column packed with glass helices, fractions being taken at 2° intervals : (i) b. p. 109—111°/3 mm. (0·64 g.), (ii) b. p. 111—113°/3 mm. (1·07 g.), (iii) b. p. 113—115°/3 mm. (1·87 g.), (iv) b. p. 115—117°/3 mm. (0·82 g.), (v) b. p. 117—119°/3 mm. (0·91 g.), and (vi) b. p. 119—121°/3 mm. (0·22 g.). All six fractions were viscid oils and as no crystallisation occurred from light petroleum (b. p. 40—60°) they were esterified separately in pyridine with *p*-nitrobenzoyl chloride (1·6, 2·7, 4·7, 2·1, 2·3, and 0·6 g., respectively) for 3 days at room temperature. After being worked up in the usual way the esters crystallised from ethanol. Seven recrystallisations of the ester obtained from fraction (i) gave (±)-*trans*-2-hydroxy*neo*menthol di-*p*-nitrobenzoate (0·08 g.), m. p. 168°, and six recrystallisations of that from fraction (vi) gave (±)-*cis*-2-hydroxy*iso*menthol di-*p*-nitrobenzoate (0·1 g.), m. p. 138°, each identical with samples previously prepared. The esters from fractions (ii)—(v), after several recrystallisations, gave a mixture of two pale yellow crystalline forms : transparent monoclinic prisms, m. p. 135—138°, and opaque (cleavage planes) rods, m. p. 145—155°. The ester samples from the four fractions were therefore combined and slow, controlled crystallisation of the total material from ethanol (60 ml.) during 5 days gave large yellow transparent monoclinic prisms (2·85 g.), m. p. 138°, and pale yellow opaque rhombohedra (3·5 g.), m. p. 145—155°, which were separated by hand-picking. Spontaneous evaporation of the mother-liquor produced fine pale yellow needles (0·25 g.), m. p. 163—164°. Recrystallisation of the needles from ethanol gave (±)-*trans*-2-hydroxy*iso*menthol di-*p*-nitrobenzoate, m. p. and mixed m. p. 166°. The prisms were

substantially pure (±)-*cis*-2-hydroxy*iso*menthol di-*p*-nitrobenzoate, the m. p. not being raised by further recrystallisation. Recrystallisation of the rhombohedra several times from ethanol gave a pure ester, m. p. 165—166°, markedly depressed on admixture with all other known di-*p*-nitrobenzoates of comparable m. p. The compound is therefore considered to be (±)-cis-2-*hydroxy*neo*menthol di*-p-*nitrobenzoate* (Found : C, 61·4; H, 5·8; N, 6·0. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%).

Reduction of Diosphenol with Lithium Aluminium Hydride.—(*a*) A solution of diosphenol (5 g.) in ether (50 ml.) was added dropwise with stirring to a suspension of lithium aluminium hydride (1 g.) in ether (25 ml.) at a rate just sufficient to maintain steady reflux. The mixture was then boiled under reflux for a further 3 hr. The excess of hydride was decomposed by water (50 ml.), the white precipitate thus produced being removed by washing with 5N-sulphuric acid (25 ml.). After washing of the ethereal solution with N-sodium hydroxide (10 ml.) and water (25 ml.) and drying ($MgSO_4$) the solvent was removed. Fractionation of the residue gave colourless oils, b. p. 90—100°/5 mm. (2·5 g.) and 120—130°/5 mm. (0·7 g.). A residue of viscid yellow oil (1 g.) remained undistilled.

(*b*) Reduction of diosphenol (5 g.) as in (*a*) but with 2 g. of lithium aluminium hydride gave colourless oils, b. p. 90—98°/3 mm. (2·7 g.) and b. p. 114—115°/3 mm. (1·1 g.), and a residue (0·8 g.).

(*c*) A solution of diosphenol (5 g.) in benzene (25 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (5 g.) in ether (25 ml.). The mixture was then heated for 3 hr. and worked up as before, giving colourless oils, b. p. 80—90°/2·5 mm. (1·1 g.) and b. p. 112—114°/2·5 mm. (2·3 g.). The still residue was negligible.

During several months the first fractions developed a very pale yellow colour and slowly deposited well-formed colourless prisms (1 g.), m. p. 159—163° (softening at 95°). The glycol fractions obtained from the reductions did not crystallise. Esterification of a small portion (0·5 g.) of the oil with *p*-nitrobenzoyl chloride (1·25 g.) in pyridine (25 ml.) gave a crude ester (oil) from which was obtained by repeated simple recrystallisation from relatively large volumes (30 ml.) of ethanol a small amount (50 mg.) of (±)-*trans*-2-hydroxy*neo*menthol di-*p*-nitrobenzoate, m. p. 168°. The crude glycol (1·6 g.), esterified with *p*-nitrobenzoyl chloride (4·0 g.) in pyridine (30 ml.) at room temperature for 4 days, gave an oil (5·0 g.). Fractional crystallisation of this from ethanol gave a small amount (0·1 g.) of (±)-*trans*-2-hydroxy*neo*menthol di-*p*-nitrobenzoate, m. p. 168°, and the *cis-neo*glycol di-*p*-nitrobenzoate, m. p. 165—166°.

The di-*p*-nitrobenzoate, m. p. 165—166° (1·5 g.), was hydrolysed for 2 hr. with potassium hydroxide (1·2 g.) in boiling methanol (15 ml.). After dilution with water (15 ml.) the methanol was removed by distillation. Next morning the glycol (60 mg.) which had crystallised as well-formed colourless flat rods, m. p. 35—45°, was filtered off. Continuous extraction (8 hr.) of the mother-liquor with ether yielded after drying ($MgSO_4$) and removal of the ether an additional quantity (0·35 g.) of the same material. The glycol, considered to be (±)-cis-2-*hydroxy*neo*menthol*, obtained pure after four recrystallisations from light petroleum (b. p. <40°), had m. p. 52° (Found : C, 68·95; H, 11·7. $C_{10}H_{20}O_2$ requires C, 69·75; H, 11·65%). Attempts to prepare a bis-3 : 5-dinitrobenzoate from the glycol failed.

(±)-cis-2-*Hydroxy*iso*menthol*.—(±)-*cis*-2-Hydroxy*iso*menthol di-*p*-nitrobenzoate (2·7 g.; m. p. 138°) was hydrolysed with potassium hydroxide (2 g.) in boiling methanol (25 ml.). After dilution with water (25 ml.) the methanol was removed by distillation and the product extracted continuously from the residue with light petroleum (b. p. 40—60°) for 4 hr. Evaporation of the solvent from the extract gave an oil (1·2 g.) which crystallised during 3 days. Three crystallisations from light petroleum (b. p. 40—60°) gave (±)-cis-2-*hydroxy*iso*menthol* (0·5 g.) as hard rosettes of fine colourless needles, m. p. 70·5—71°, which sublimed slowly at room temperature forming long fibres (Found : C, 70·0; H, 11·8%).

This glycol (0·1 g.) was boiled under reflux for 0·5 hr. with 3 : 5-dinitrobenzoyl chloride (0·3 g.) and pyridine (3 ml.) in benzene (15 ml.) and then set aside for 24 hr. Three recrystallisations of the crude ester from benzene–light petroleum (b. p. 40—60°) gave (±)-cis-2-*hydroxy*-iso*menthol bis*-3 : 5-*dinitrobenzoate* as clusters of pale yellow needles, m. p. 143° (Found : C, 51·6; H, 4·6; N, 9·7. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3; N, 10·0%).

JOHNSON CHEMICAL LABORATORIES,
UNIVERSITY OF ADELAIDE.

[*Received, July 29th*, 1953.]

p-*Menthane*-2 : 3-*diols. Part IV.* The Reaction of Mercuric Acetate with* (±)-*Menthone and* (±)-iso*Menthone.*

By P. R. Jefferies, A. Killen Macbeth, and B. Milligan.

[Reprint Order No. 4699.]

Treatment of either (±)-menthone or (±)-*iso*menthone with mercuric acetate in acetic acid yields predominantly (±)-2-acetoxymenthone in addition to a small amount of (possibly) a (±)-4-acetoxymenthone. Reduction of this mixture of acetoxymenthones by sodium in ethanol yields (±)-*trans*-2-hydroxymenthol and possibly a (±)-*p*-menthane-3 : 4-diol; catalytic hydrogenation of the mixed hydroxymenthones yields (±)-*cis*- and (±)-*trans*-2-hydroxy*neo*menthol, and an unidentified *p*-menthane-diol.

By treatment of (−)-menthone with mercuric acetate in acetic acid, Treibs and Bast (*Annalen*, 1948, **561**, 165) prepared an optically active 2-acetoxymenthone which on hydrolysis gave a practically inactive 2-hydroxymenthone. Reduction with sodium in ethanol yielded a crystalline diol.

It was hoped that reduction of (±)-2-acetoxymenthone and (±)-2-acetoxy*iso*menthone by sodium in ethanol and catalytic hydrogenation of the corresponding hydroxy-compounds would provide another route to the (±)-*p*-menthane-2 : 3-diols, thus affording additional evidence concerning the configurations assigned by Macbeth and Robertson (*J.*, 1953, 895; Parts II and III *) to the eight epimeric (±)-*p*-menthane-2 : 3-diols.

We have repeated the reduction of acetoxy-(−)-menthone (Treibs and Bast, *loc. cit.*) and purified the resultant diol *via* its di-*p*-nitrobenzoate, m. p. 117°. Both the diol and its diester were optically inactive, racemisation apparently taking place during the sodium–ethanol reduction. Thus it is not possible to obtain the active *p*-menthane-2 : 3-diols by reactions analogous to those described above.

When (±)-menthone was added to a boiling solution of mercuric acetate in acetic acid, the characteristic crystalline mercury complex separated immediately; it was decomposed at 130° with the formation of metallic mercury and (±)-2-acetoxymenthone, which was characterised as the 2 : 4-dinitrophenylhydrazone. An identical reaction with (±)-*iso*menthone gave a product similar in physical properties to (±)-2-acetoxymenthone and forming the same 2 : 4-dinitrophenylhydrazone. Chemical reduction and catalytic hydrogenation of both products yielded menthols and *p*-menthane-2 : 3-diols corresponding to the menthone, as opposed to the *iso*menthone, series. Thus it appears that an equilibrium mixture consisting predominantly of (±)-2-acetoxymenthone is obtained from the Treibs–Bast reaction with both (±)-menthone and (±)-*iso*menthone. The isolation in small amount of what is possibly a (±)-*p*-menthane-3 : 4-diol leads us to believe that the acetoxy-group is also introduced, to a very limited extent, in the 4-position, contrary to the statement by Treibs and Bast (*loc. cit.*) that tertiary attack does not occur.

Inversion appears to take place during the mercuric acetate reaction, and might either precede the formation of the crystalline mercury complex or occur after its decomposition. Menthones are converted into their addition complexes in about 3 minutes, and measurements of rotation of the active menthones (see Table) show that inappreciable inversion of

Time of reflux with acetic acid (min.)	(−)-Menthone, α_D^{15} −25·7°		(+)-*iso*Menthone, α_D^{15} +82·1°	
	α_D^{15}	Composition, menthone–*iso*menthone	α_D^{15}	Composition, menthone–*iso*menthone
3 Min.	−22·7°	97·2%; 2·8%	+74·9°	6·7%; 93·3%
2 Hr.	+11·2°	65·8%; 34·2%	+17·6°	59·9%; 40·1%

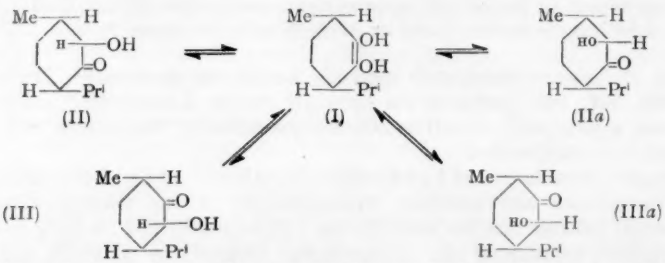
menthone and *iso*menthone occurs within this period. The inversion, catalysed by acetic acid, therefore probably occurs between 2-acetoxymenthone and 2-acetoxy*iso*menthone, and greatly favours the former.

Hydrolysis of the acetoxymenthone mixtures yielded the corresponding acyloins as

* Parts II and III, *J.*, 1953, 3512; 1954, 701.

colourless oils of wide boiling range. Their heterogeneity may be explained by assuming inversion *via* the enolic form (I) during hydrolysis, resulting in a mixture of 2-hydroxymenthones (II ⟷ II*a*), and possibly 3-hydroxycarvomenthones (III ⟷ III*a*). The existence of (I) was shown by the isolation of its di-*p*-nitrobenzoate.

The Treibs–Bast reaction has been applied to a number of terpene ketones but the configuration of the acetoxylated products does not appear to have been established. Introduction of the acetoxy-group in the *trans*-relation to the methyl group is now shown in the case of acetoxy-menthone and *-iso*menthone, by reduction with sodium in ethanol, the main product being (±)-*trans*-2-hydroxymenthol. Hydrolysis of the acetoxy-group probably occurs simultaneously with reduction of the carbonyl group, and thus inversion at the 2-position is inhibited.



Distillation of the sodium–ethanol reduction product of the acetoxy-(±)-menthones yielded a mobile fore-run, and a very viscid oil as the main fraction, whence (±)-*trans*-2-hydroxymenthol was isolated. Chromatography of an ester prepared from the remainder of the main fraction yielded two di-*p*-nitrobenzoates of this diol and, in very small amount, of the supposed (±)-*p*-menthane-3 : 4-diol (glycol C) obtained from the peracetic acid oxidation of (±)-*p*-menth-3-ene (Macbeth and Robertson, *loc. cit.*). (±)-Menthol was isolated from the fore-run as its *p*-nitrobenzoate.

Hydrogenation of the inversion mixture of hydroxymenthones, derived from either (±)-menthone or (±)-*iso*menthone, at high temperature and pressure in presence of copper chromite, yielded, in addition to an unidentified hydrocarbon, (±)-*cis*-2-hydroxy*neo*-menthol isolated as its di-*p*-nitrobenzoate by chromatography. This diol has been prepared by both Ponndorf and lithium aluminium hydride reduction of diosphenol (Part III), and the unidentified hydrocarbon is probably *trans*-*p*-menthane, produced by hydrogenolysis.

Raney nickel (activity W 7) has also been used as a catalyst for hydrogenations carried out at room temperature and pressure. The products formed were separated by chromatography of their di-*p*-nitrobenzoates into esters of a diol, $C_{10}H_{20}O_2$, of (±)-*cis*- and of (±)-*trans*-2-hydroxy*neo*menthol. A mixed di-*p*-nitrobenzoate fraction yielded the first of these esters as well as an unidentified compound. These unknown esters, which may be derived from the (±)-*p*-menthane-3 : 4-diols, are being further examined.

Hydrogenation with platinum oxide at room temperature was unsatisfactory.

Experimental

Unless otherwise stated, light petroleum had b. p. 60—70°, and B.D.H. alumina for chromatographic absorption was used.

Acetoxylation of (±)-*Menthone.*—(±)-Menthone (38 g.) was added to a solution obtained by dissolving mercuric oxide (53 g.) in boiling glacial acetic acid (50 ml.). Acetic acid was removed by distillation until the temperature of the mixture rose to 130°, boiling under reflux being then resumed for 2 hr. After decantation from the liberated mercury, the mixture was neutralised with sodium hydrogen carbonate solution and extracted with ether. Distillation gave a fore-fraction of menthone (10·9 g.) and a mixture of acetoxymenthones (20·8 g., 62% based on menthone used), b. p. 120·5—122·5°/6 mm., d_4^{20} 1·0204, n_D^{20} 1·4625, $[R_L]_D$ 57·2 (calc. 57·2) (Found: C, 68·4; H, 9·5. Calc. for $C_{12}H_{20}O_3$: C, 67·9; H, 9·5%).

Acetoxylation of (±)-iso*Menthone.*—(±)-*iso*Menthone (38 g.), treated as above, gave un-

changed *iso*menthone (13·7 g.) and a mixture of acetoxymenthones (21·0 g., 71% based on *iso*menthone used), b. p. 102—104°/2 mm., d_4^{20} 1·0204, n_D^{20} 1·4615, $[R_L]_D$ 57·0 (calc. 57·2) (Found : C, 68·2; H, 9·4%).

2 : 4-*Dinitrophenylhydrazones* prepared from each of the above samples crystallised from light petroleum–benzene as yellow needles, m. p. 190° (Found : C, 55·0; H, 6·0; N, 13·6. $C_{18}H_{24}O_6N_4$ requires C, 55·1; H, 6·1; N, 14·0%).

Hydrolysis of the Inversion Mixture of Acetoxymenthones.—The above mixture (20 g.) was refluxed with a solution of potassium hydroxide (20 g.) in water (200 ml.) for 0·3 hr. The product was thrice extracted with ether and on distillation gave mixed (±)-2-hydroxymenthones (14·0 g., 87%), b. p. 102—114°/3·0 mm. Esterification of this (2·0 g.) with a 200% excess of *p*-nitrobenzoyl chloride in boiling pyridine for 2 hr. gave an oil which was chromatographed in petroleum–benzene (1 : 1); elution with the same solvent (500 ml.) gave the crude ester (1·0 g.) which after three crystallisations from light petroleum formed needles of the *di*-p-*nitrobenzoate* of the diol (I), having m. p. 147° (Found : C, 62·0; H, 4·9; N, 6·0. $C_{24}H_{24}O_8N_2$ requires C, 61·55; H, 5·1; N, 6·0%).

Sodium–Ethanol Reduction of the Inversion Mixture of (±)-2-*Acetoxymenthones*.—Metallic sodium (15 g.) was added in small portions to a solution of acetoxymenthones (12·8 g.) in boiling ethanol (140 ml.). More ethanol (80 ml.) was added during the reduction to maintain a homogeneous solution. Water (100 ml.) was then added, and the ethanol removed by fractional distillation. The aqueous residue was thrice extracted with light petroleum, and the combined extracts were washed with water and dried ($MgSO_4$). Distillation gave a mobile fore-run (2·4 g.), b. p. 70—96°/5 mm., and a viscid fraction (4·8 g.), b. p. 96—100°/5 mm. Crystals (0·2 g.) were deposited from the latter fraction, and were drained on a tile and crystallised twice from light petroleum (b. p. <40°), forming colourless prisms, m. p. 90·5°, undepressed on admixture with an authentic sample of (±)-*trans*-2-hydroxymenthol.

The non-crystalline portion (4·6 g.) of the high-boiling fraction gave a crude ester (11·7 g., 93%) on esterification with *p*-nitrobenzoyl chloride in pyridine. The ester was chromatographed in light petroleum–benzene (20 : 1) on alumina (200 g.). Elution with light petroleum–benzene (5 : 1) gave a di-*p*-nitrobenzoate (3·0 g.) as pale yellow needles, m. p. 117° (after two crystallisations from methanol). The m. p. was undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*trans*-2-hydroxymenthol. Hydrolysis with methanolic potassium hydroxide gave (±)-*trans*-2-hydroxymenthol, m. p. 90·5° after one crystallisation from light petroleum (b. p. <40°). Elution of the chromatogram with benzene gave pale yellow prisms (75 mg.), m. p. 137° after five crystallisations from methanol. The m. p. was undepressed on admixture with a sample of di-*p*-nitrobenzoate of a diol derived from (±)-*p*-menth-3-ene by peracetic acid hydroxylation.

Esterification of the mobile fraction (2·4 g.) of the distillate with *p*-nitrobenzoyl chloride in pyridine yielded a crude ester (3·5 g.) from which (±)-menthyl *p*-nitrobenzoate, m. p. 91° (0·5 g.), was obtained after crystallisation from methanol.

Hydrogenation of the Inversion Mixture of (±)-*Hydroxymenthones*.—(*a*) The above inversion mixture (5 g.) was hydrogenated at an initial pressure of 1000 lb./in.^{2} and 200—230° for 6 hr. with copper chromite (0·5 g.; *Org. Synth.*, **19**, 31). Ether (50 ml.) was added, and the catalyst removed by filtration. The ethereal solution was dried ($MgSO_4$) and evaporated, and the product (4·3 g., 86%) esterified with *p*-nitrobenzoyl chloride in pyridine. After steam-distillation to remove hydrocarbon, the crude ester (5·0 g., 43%) was chromatographed in light petroleum–benzene (5 : 1) and on alumina (100 g.). Elution with light petroleum–benzene mixtures afforded oils, but benzene eluted a crystalline ester (0·3 g.) which, crystallised three times from methanol, formed pale yellow prisms (0·15 g.), m. p. 166° alone or mixed with the di-*p*-nitrobenzoate (m. p. 166—167°) of (±)-*cis*-2-hydroxy*neo*menthol.

(*b*) A solution of the inversion mixture of hydroxymenthones (5 g.) in ethanol (100 ml.) was hydrogenated at room temperature and pressure with Raney nickel catalyst (activity W 7; *Org. Synth.*, **29**, 28). Uptake was 90% after 4·5 hr. After removal of the catalyst, water (60 ml.) was added, and the ethanol removed by fractional distillation. The product was continuously extracted overnight with ether and isolated as a yellow oil (4·1 g., 82%) which was esterified with *p*-nitrobenzoyl chloride in pyridine. The crude ester (7·8 g., 68%), a viscid yellow oil, was chromatographed in light petroleum–benzene (10 : 1) on alumina (150 g.). The esters obtained, in order of elution, were (i) with light petroleum–benzene (10 : 1) a *di*-p-*nitrobenzoate* of a diol, $C_{10}H_{20}O_2$, which crystallised from methanol as pale yellow prisms (200 mg.), m. p. 155° (Found: C, 61·4; H, 5·7. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%); (ii) with light petroleum–benzene (4 : 1) a di-*p*-nitrobenzoate of a diol, $C_{10}H_{20}O_2$, which crystallised as short

pale yellow prisms (200 mg.), m. p. 122° (Found: C, 61·3; H, 5·5; N, 6·0%). Further crystallisation from light petroleum gave a mixture of pale yellow prisms and long white needles which were separated by hand-picking. The prisms (30 mg.) had constant m. p. (155°) after four crystallisations from light petroleum; the m. p. was undepressed on admixture with a sample of the di-*p*-nitrobenzoate (i), m. p. 155°. The white needles (15 mg.) had m. p. 105° after four crystallisations from light petroleum (Found: C, 62·4; H, 5·7%); (iii) with benzene a di-*p*-nitrobenzoate, which also crystallised from methanol as pale yellow prisms (100 mg.), m. p. 165°, undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*cis*-2-hydroxy*neo*menthol; (iv) with benzene–ether (100 : 1) pale yellow plates (50 mg.), m. p. 166° after three crystallisations from methanol. The m. p. was undepressed on admixture with an authentic sample of the di-*p*-nitrobenzoate of (±)-*trans*-2-hydroxy*neo*menthol.

(*c*) The inversion mixture of (±)-hydroxymenthones (5 g.) in glacial acetic acid (30 ml.) containing concentrated hydrochloric acid (2 drops) was hydrogenated with platinum oxide (0·5 g.) at room temperature and pressure. Hydrogenation ceased after 3 hr., being 50% complete. After filtration, the mixture was basified with sodium hydroxide and boiled under reflux for 30 min. to hydrolyse any acetates produced during the hydrogenation. The mixture was continuously extracted with ether, and the product (4·8 g., 96%) thus isolated was esterified with *p*-nitrobenzoyl chloride in pyridine. The crude ester (7·6 g., 57%) was chromatographed in light petroleum–benzene (4 : 1) on alumina (150 g.); elution with the same solvent yielded a crystalline ester (100 mg.), m. p. 122° after four crystallisations from methanol. There was no depression of m. p. on admixture with a sample of the mixed crystals, m. p. 122°, obtained in the previous hydrogenation. Other fractions from the chromatogram could not be induced to crystallise.

We are indebted to Dr. W. G. P. Robertson for helpful suggestions, and thank Messrs. Plaimar Ltd. for a gift of menthol.

JOHNSON CHEMICAL LABORATORIES
THE UNIVERSITY OF ADELAIDE, AUSTRALIA. [*Received, October 5th,* 1953.]

The Relation between Self-condensation and Substitution Processes in the Reactions of meso*Benzanthrone with Anions.*

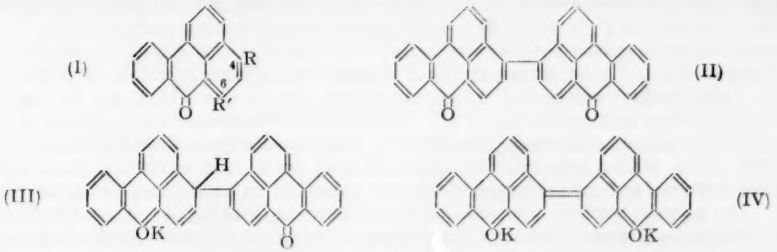
By WILLIAM BRADLEY and F. K. SUTCLIFFE.

[Reprint Order No. 4774.]

Experiments with *meso*benzanthrone and a series of anions have shown that anions which have the greatest tendency to form covalent links with carbonyl-carbon (*e.g.*, Ph^-, NH_2^-) react by replacing nuclear hydrogen *ortho* or *para* to the carbonyl group. Anions of higher electron affinity (*e.g.*, OH^-, OR^-) function mainly as bases and cause the conversion of *meso*benzanthrone into 4 : 4′-di*meso*benzanthronyl.

PREVIOUS work has shown that *meso*benzanthrone (I; R = R′ = H) reacts with the anions of weak acids and other bases in one or both of two ways. Nuclear hydrogen situated *ortho* or *para* to the carbonyl group may be replaced by the reagent, or self-coupling of *meso*benzanthrone may occur with the formation of 4 : 4′-di*meso*benzanthronyl (II). The relative importance of the substitution and the self-coupling reaction depends on the reagent employed. Potassium hydroxide in methanol, ethanol, or *iso*propanol at 100—150° gives mainly (II) accompanied by a small amount of 4-hydroxy*meso*-benzanthrone (I; R = OH, R′ = H), sodioaniline in aniline at 40° gives 4-anilino*meso*-benzanthrone (I; R = Ph·NH, R′ = H) and 50% of (II) (Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 259), but sodamide gives 6-amino*meso*benzanthrone (I; R = H, R′ = NH_2) with no appreciable amount of (II) (Bradley, *J.*, 1948, 1175). From these results it appears that the anions which are most active in forming covalent bonds with carbonyl-carbon, *e.g.*, NH_2^-, bring about substitution, whilst those which are less active in this respect, *e.g.*, OH^-, function mainly as bases and cause the ionisation of *meso*benzanthrone, so leading to the formation of (II) by the action of the resulting *meso*benzanthrone

anion on undissociated *meso*benzanthrone (Bradley and Jadhav, *J.*, 1948, **1622**; Bradley and Sutcliffe, *J.*, 1952, **1247**). In agreement with this view anions of intermediate activity, *e.g.*, $Ph{\cdot}NH^-$, bring about both substitution and self-condensation simultaneously. These relations have been tested and confirmed in the following experiments, which also indicate the nature of the products that first result from the action of active anions on *meso*benzanthrone. Potassium *tert.*-butoxide in *tert.*-butanol at 90—92° converted (I; R = R′ = H) into (II), only a trace of 4-hydroxy*meso*benzanthrone being formed. Similar results were obtained with potassium *iso*propoxide in *iso*propanol, but potassium phenoxide was without effect. The results with the two alkoxides accord with those of Lüttringhaus and Neresheimer (*loc. cit.*), and it has also been shown that the formation of (II) occurs without evolution of hydrogen, and that when the first reaction is complete the resulting products absorb oxygen. Oxidation implies the intermediate formation



of a reduced state of (II), and this could result by the self-addition of two molecules of *meso*benzanthrone to give such structures as (III) and (IV). In this connection reference should be made to the work of Koelsch and Anther (*J. Org. Chem.*, 1941, **6**, 558) who showed that perinaphthenone reacts with phenylmagnesium bromide to give a dihydroaromatic compound.

Using sodioaniline in aniline at the room temperature we obtained the same result as Lüttringhaus and Neresheimer (*loc. cit.*) at 40°. With sodiodiphenylamine in benzene at 80° self-coupling and substitution occurred, 4-diphenylamino*meso*benzanthrone (I; R = Ph_2N, R′ = H) and (II) resulting. Self-coupling was the more important reaction and the yield of (II) accorded with the smaller basic strength of diphenylamine in relation to aniline and the corresponding smaller tendency of its anion to form a covalent link—Conant and Wheland (*J. Amer. Chem. Soc.*, 1932, **54**, 1212) and McEwen (*ibid.*, 1936, **58**, 1124) have recorded the following values of pK on an arbitrary scale; phenol, 10; methanol, 16; ethanol, 18; *tert.*-butanol, 19; diphenylamine, 23; aniline, 27; triphenylmethane, 33. There was no evolution of hydrogen when either sodioaniline or sodiodiphenylamine was used, thus confirming the additive character of the self-condensation and the substitution process under the conditions employed. The reaction with sodiodiphenylamine did not take place in ether.

In accord with the feeble acid strength (Brönsted) of benzene and the relation referred to, phenylsodium gave 6-phenyl*meso*benzanthrone (I; R = H, R′ = Ph) (Allen and Overbaugh, *J. Amer. Chem. Soc.*, 1935, **57**, 740), but there was no indication of the formation of (II); nor was there a reaction between *meso*benzanthrone and triphenylmethylsodium, possibly on account of steric factors.

Experimental

meso*Benzanthrone and Potassium* tert.*-Butoxide.*—*meso*Benzanthrone (10 g.) was heated and stirred for an hour at 92° (internal temperature), in an atmosphere of nitrogen, with a solution of potassium *tert.*-butoxide prepared from potassium (15·6 g.) and *tert.*-butanol (250 c.c.). Water was then added, the nitrogen was replaced by oxygen, and stirring was continued. Absorption of oxygen occurred and when it was complete more water was added. A solid separated and this was collected, washed, dried (yield, 7·1 g.), and identified as 4 : 4′-di*meso*-benzanthronyl, m. p. 315°.

In a similar experiment in which *meso*benzanthrone (10 g.) was stirred for an hour at 90—

92° with potassium *iso*propoxide prepared from potassium (15·6 g.) and *iso*propanol (122 c.c.), it was shown that no evolution of gas occurred during the reaction, and that on the further addition of water, admission of oxygen, filtration, and purification of the alkali-insoluble product, the yield of 4 : 4′-di*meso*benzanthronyl, m. p. 313°, was 5·0 g. In this experiment the alkaline filtrate yielded 0·1 g. of 4-hydroxy*meso*benzanthrone.

*meso*Benzanthrone (1 g.) was recovered unaltered after 1·5 hours' heating with potassium hydroxide (3 g.) in phenol (10 g.).

meso*Benzanthrone and Sodioaniline.*—As directed by Lüttringhaus and Neresheimer (*loc. cit.*) *meso*benzanthrone (7·5 g.) was added at the room temperature to a solution prepared by refluxing sodium (2·5 g.) with " AnalaR " aniline (50 c.c.) in nitrogen for 2·5 hr. The reactants were stirred for 4 hr.; there was no rise in temperature or evolution of hydrogen. Alcohol (50 c.c.) and then water (200 c.c.) were added, and again no evolution of gas occurred. When the nitrogen was replaced by oxygen, however, absorption occurred. When the reaction was complete the products were 4 : 4′-di*meso*benzanthronyl (2·9 g.; m. p. 315°) and 4-anilino-*meso*benzanthrone (3·2 g.; m. p. 214—215°, after recrystallisation from xylene).

meso*Benzanthrone and Sodiodiphenylamine.*—(*a*) Sodamide (8 g.), diphenylamine (150 g.), and benzene (75 c.c.) were stirred and heated under reflux until evolution of ammonia ceased (2 hr.). The product was cooled, *meso*benzanthrone (10 g.) was added, and stirring was continued at the room temperature for 24 hr. There was no evolution of gas at this stage. Alcohol (100 c.c.) was added, and steam was admitted until all unchanged diphenylamine had been removed. The residue was collected, washed, and dried. On extraction with acetone an insoluble portion (4·75 g.) remained which was identified as 4 : 4′-di*meso*benzanthronyl, m. p. 313°. The soluble fraction was isolated and passed in benzene down an alumina column (50 × 2·5 cm.). The adsorbed band was developed by means of benzene and the main, reddish-brown portion was separated and eluted with acetone. The extract gave 3·5 g. of an orange-brown solid, m. p. 147—170°. This was separated by chromatography from benzene on alumina into two orange-brown bands. The more strongly retained afforded *meso*benzanthrone (1 g.), m. p. 170—172°. The lower band was a product which, eluted and crystallised from benzene, formed small, orange-yellow needles (1·6 g.), m. p. 200—202° (Found: C, 87·2; H, 4·8; N, 3·8. $C_{29}H_{19}ON$ requires C, 87·7; H, 4·9; N, 3·6%), identical with 4-*diphenylamino*meso-*benzanthrone* prepared from 4-iodo*meso*benzanthrone and diphenylamine. It showed light absorption maxima in " AnalaR " pyridine at 3980 (ε 7400) and 4680 Å (ε 15,400).

(*b*) Sodamide (8 g.), diphenylamine (33·8 g.), and dry ether (200 c.c.) were stirred at the room temperature and then refluxed. When the evolution of ammonia ceased (2 hr.), *meso*-benzanthrone (10 g.) and ether (50 c.c.) were added, and the stirring and heating were resumed for 3 hr. There was no evidence of reaction; 8·5 g. of *meso*benzanthrone, m. p. 171—172°, were recovered.

4-*Diphenylamino*meso*benzanthrone.*—Diphenylamine (2 g.), 4-iodo*meso*benzanthrone (0·5 g.), copper bronze (0·01 g.), and nitrobenzene (5 c.c.) were heated under reflux for 5 hr. and then distilled in steam. The residual dark tar was extracted with benzene, the solution was chromatographed on alumina, and the adsorbed band was developed with benzene. An orange band passed through the column and from this was obtained 4-diphenylamino*meso*benzanthrone, m. p. 198—200°, identical with the same compound described under (*a*).

meso*Benzanthrone and Phenylsodium.*—As instructed by Gilman (*J. Amer. Chem. Soc.*, 1940, **62**, 1514) phenylsodium was prepared under nitrogen, below 40°, by adding bromobenzene (31·4 g.) to powdered sodium (9·2 g.) in dry benzene (100 c.c.). *meso*Benzanthrone (10 g.) was added and the reactants were stirred at the room temperature for 3 hr. No evolution of gas or rise in temperature was noted. Alcohol (50 c.c.) and water (200 c.c.) were added, the nitrogen was replaced by oxygen, and the products were vigorously stirred. The benzene layer was separated, washed with water, and distilled in steam, finally in superheated steam. The residue was a green, resinous mass and this was dissolved in benzene and chromatographed on a column of alumina (30 × 2·5 cm.). On treatment with benzene first a green, then a brown, band passed through the column, leaving behind a main brown band; this was eluted with benzene containing 5% by volume of methanol. The solutes were isolated from the three eluates and each was stirred with ether and yielded a quantity of brownish-yellow crystals. These were collected, combined (1·5 g.), and recrystallised from benzene (m. p. 186—188°). The ether-soluble materials were similarly isolated, combined, and heated in a molecular still at approx. 200—230°/10^{-5} mm. The orange, resinous distillate (4 g.), when stirred with ether, gave a solid, and this after purification from benzene afforded an additional 1·3 g. of crystals, m. p. 182—185°. The two crops of crystals were united and then recrystallised from benzene

(charcoal). 6-Phenyl*meso*benzanthrone, m. p. 187—187·5°, was obtained, identical with the compound prepared from *meso*benzanthrone and phenylmagnesium bromide (Allen and Overbaugh, *loc. cit.*). In solution in "AnalaR" pyridine the 6-phenyl*meso*benzanthrone showed maximum light absorption at 3640 (ε 8100) and 3900 Å (ε 9300).

There was no reaction when triphenylmethylsodium, prepared from triphenylmethyl chloride (27·8 g.) according to *Org. Synth.*, Coll. Vol. II, p. 607, was added to a suspension of *meso*benzanthrone (10 g.) in benzene (50 c.c.), or when benzene (100 c.c.) was added subsequently, the ether being removed by distillation, and the reactants were heated for a further 4 hr.

CLOTHWORKERS' RESEARCH LABORATORY,
UNIVERSITY OF LEEDS.

[*Received, November 9th,* 1953.]

Glow-discharge Electrolysis. Part II. The Anodic Oxidation of Ferrous Sulphate.*

By A. HICKLING and J. K. LINACRE.

[Reprint Order No. 4465.]

The electrolysis of ferrous sulphate solutions in dilute sulphuric acid has been investigated by use of a glow-discharge anode. Oxidation of the ferrous salt occurs, accompanied by marked evolution of hydrogen from the solution, and it appears that much of the oxidation arises from the dissociation of water molecules owing to bombardment of the solution by positive gaseous ions. The phenomena are closely similar to the effects produced by ionising radiations in solution, particularly α-rays, although in the present work comparatively low-energy particles at high dose rates are involved. The oxidation yield (G, in equivalents per faraday) depends upon the concentration of ferrous sulphate, the nature of the electrolyte, the temperature, and the presence of oxygen, but is otherwise independent of most experimental variables; it can be represented by an equation, which has been deduced theoretically, of the form

$$G = 1 + n([Fe^{++}] + A)/([Fe^{++}] + A + B)$$

where n is the number of equivalents of oxidising agent formed per faraday by the dissociation of water, and A and B are constants, which can be evaluated, for any given set of experimental conditions. Most of the experimental results can be simply explained on the assumption that the OH radical is the primary oxidising species, but the action of inert salts in raising the oxidation yield suggests that the H_2O^+ ion may possibly play a direct part in the oxidation.

THE present investigation was undertaken to ascertain the nature of the anodic process in the glow-discharge electrolysis of an easily oxidisable ion. The results show, however, that the oxidation brought about electrolytically is overshadowed by that arising from the ionisation and dissociation of water molecules. This is brought about apparently by the entry of positively charged gaseous ions into the aqueous solution in carrying the current, and the chemical effects produced have many features in common with those observed in the study of he effect of ionising radiations on ferrous salt solutions. (See, *e.g.*, for X- *and* γ-*rays*: Fricke, *Phys. Review*, 1928, **31**, 1117; Fricke and Morse, *Phil. Mag.*, 1929, **7**, 129; Shishacow, *ibid.*, 1932, **14**, 198; Fricke and Hart, *J. Chem. Phys.*, 1935, **3**, 60; Krenz and Dewhurst, *ibid.*, 1949, **17**, 1337; Miller, *ibid.*, 1950, **18**, 79; Rigg, Stein, and Weiss, *Proc. Roy. Soc.*, 1952, *A*, **211**, 375; Amphlett, *Discuss. Faraday Soc.*, 1952, **12**, 144; Hardwick, *ibid.*, p. 203; Miller and Wilkinson, *ibid.*, p. 50. For α-*rays*: Nurnberger, *J. Phys. Chem.*, 1934, **38**, 47; Miller and Wilkinson, *Discuss. Faraday Soc.*, 1952, **12**, 110. For *neutrons*: Wright, *ibid.*, p. 60. For β-*rays*: Hardwick, *Canadian J. Chem.*, 1952, **30**, 39.) In glow-discharge electrolysis the energy of the particles entering the solution is relatively very low, but they can be supplied at very high and accurately controlled rates, and the present

* Part I, *J.*, 1952, 3595.

technique thus affords an easy method of studying the chemical behaviour of radicals derived from water molecules.

Experimental

An H-shaped cell was used as shown in Fig. 1. It consisted of two cylindrical glass vessels, which formed the anode and cathode compartments, joined by short side tubes near the bottom. The anolyte and catholyte were prevented from mixing by a filter-paper plug in the side tube of the anode compartment, and the two halves of the cell were connected by a short length of rubber tubing. The height of the cell was about 13 cm., and except where otherwise stated an anode compartment with a cross-sectional area of 10 sq. cm. was used. The compartments were closed by rubber bungs which carried the cell components. The anode, from which the discharge occurred, was of platinum wire connected to a tungsten rod sealed into a glass holder; the cathode was a small sheet of platinum foil of approximately 1 sq. cm. area. The anode and the cathode compartment were separately connected to the vacuum line through small ground-glass joints, which permitted easy removal of the cell. In most cases the anolyte was stirred during electrolysis by a small rotor magnet enclosed in a plastic case; this was rotated from beneath by means of a strong bar magnet mounted on an electric motor. To remove the

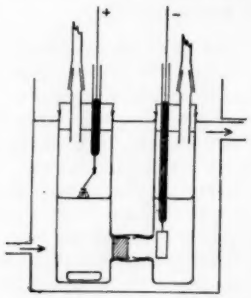


Fig. 1. *Cell for glow-discharge oxidation.*

considerable heat dissipated in the discharge, the cell was almost completely immersed in a bath through which a rapid stream of tap water was passed; under usual conditions the bulk temperature could be kept fairly steady at 18° by this means.

The vacuum system was of a conventional type but included a float manostat so that the pressure in the apparatus could be kept constant over long periods. Before each electrolysis the pressure was reduced until the anolyte boiled, and the cell was then filled with nitrogen from a reservoir bulb; the pressure was then again reduced and maintained at any desired value throughout electrolysis. Where it was desired to estimate the gaseous anode products, the anode compartment was isolated from the vacuum line and connected to a Toepler pump; after initial evacuation, the pressure was allowed to rise to the desired value and was then kept steady by pumping off the anode gases as formed and collecting them over mercury in a glass hood. At the end of electrolysis the cell was again evacuated and the total volume of gas was measured in a gas burette; samples were then analysed in a Bone–Newitt apparatus.

The electrical circuit was essentially as previously described and consisted of a Leland rectifier unit of adjustable voltage (0—1500 v) connected to the cell through a calibrated milliammeter and suitable ballast resistance (2000—10,000 ohms). The discharge was initiated by a pulse from an induction coil, and took the form of a sharply defined cone between the tip of the anode and the electrolyte surface; once started, the discharge required about 600 v, and the current could be kept steady at any desired value in the range 0·025—0·10 a.

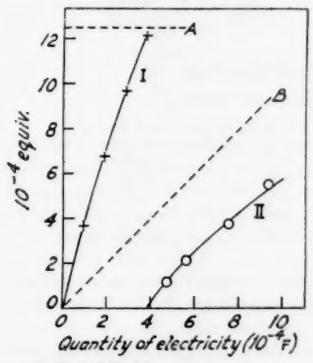
The anolyte was a solution of ferrous sulphate in a sulphuric acid medium; the catholyte was sulphuric acid alone. As preliminary experiments showed that the glow-discharge oxidation was in many respects similar to that produced by ionising radiations, a 0·8n-sulphuric acid solution was used in most cases to conform with the majority of work in the radiation field. "AnalaR" reagents were employed in preparing the electrolyte, which was gassed out with nitrogen before use. The amount of ferrous ion oxidised was determined by titration with 0·025n-potassium permanganate before and after electrolysis. In the absence of ferrous ions or after their complete oxidation, hydrogen peroxide was formed in the anolyte as indicated by reaction with titanic sulphate; the hydrogen peroxide was also estimated by permanganate titration.

The experimental conditions usually employed were: Anolyte, 50 ml. of stirred 0·025M-ferrous sulphate in 0·8N-sulphuric acid; anode, platinum wire with its tip 0·75 cm. from the electrolyte surface; current, 0·075 amp.; pressure of nitrogen in cell, 50 mm.; temp., *ca.* 18°. These are referred to as the " standard conditions " and are to be taken to apply when the experimental variables are not otherwise specified.

Results

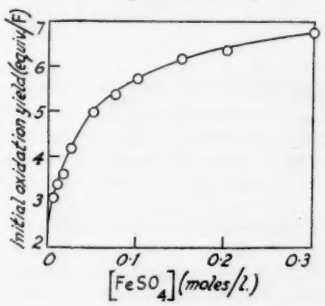
Influence of General Factors.—Quantity of electricity. In Fig. 2 are shown the results of a series of experiments in which 0·025M-ferrous sulphate in 0·8N-sulphuric acid was electrolysed under standard conditions for various times; the number of equivs. of ferrous ion oxidised and hydrogen peroxide produced are plotted against the quantity of electricity passed expressed in faradays. It is seen that oxidation of ferrous ion takes place from the start of electrolysis but the amount oxidised is much greater than the yield of 1 equiv./faraday expected from Faraday's laws. The initial instantaneous or differential yield, as given by a tangent to the curve, is 4·2 equivs./faraday, and this decreases during electrolysis to a final value of 2·5 as the last of the ferrous sulphate is used up. At this point formation of hydrogen peroxide begins and it proceeds exactly as for the sulphuric acid medium alone, ultimately attaining a stationary concentration when it is being decomposed as fast as it is formed (see Part I).

Fig. 2. *Glow-discharge oxidation of ferrous ion.*



A, Total Fe^{++} present.
B, Theoretical electrolytic yield.
I, Fe^{++} oxidised.
II, H_2O_2 formed.

Fig. 3. *Influence of ferrous-ion concentration upon oxidation yield.*



Current. In Table 1 are shown the amounts of ferrous ion oxidised for increasing quantities of electricity at each of four currents (0·10, 0·075, 0·05, and 0·025 A) severally; a pressure

Table 1. *Influence of current on oxidation of ferrous ion.*

Quantity of electricity (10^{-4} F)	Fe^{++} oxidised (10^{-4} equiv.)			
	0·10 A	0·075 A	0·05 A	0·025 A
0·93	3·57	3·60	3·77	3·77
1·86	7·12	6·90	6·90	6·90
2·80	10·17	9·92	10·00	9·67
3·73	12·77	12·23	12·35	11·75

of 25 mm. was used, as the discharge at the lowest current was more stable at low pressures. In spite of the very different electrical power dissipated at the different currents, and the different times of electrolysis involved, the oxidation yields are practically the same for equal quantities of electricity passed. This indicates very clearly that whatever is the mechanism of the oxidation it is primarily dependent upon the quantity of electricity passed.

Volume, surface area, and stirring of anolyte. A selection of the results obtained by variation of these factors is given in Table 2. The amount of ferrous ion oxidised appears to be independent of the volume of the anolyte in the early stages of electrolysis; for the passage of greater quantities of electricity, it increases slightly the larger the volume of the anolyte, but this is simply

due to the higher ferrous-ion concentration then existing, and at comparable concentrations no volume effect could be detected. Similarly, variation of the surface area of the anolyte has no marked effect upon the course of the oxidation; experiments carried out with surface areas of 10 and 19 sq. cm. show that for equal quantities of electricity the amount of ferrous ion oxidised is substantially the same. Stirring has little influence upon the oxidation in its early stages, but as it nears completion the unstirred solution gives lower yields. This was found to be due to the premature build-up of a stationary concentration of hydrogen peroxide in the surface of the anolyte before all the ferrous ion in the bulk of the solution had been oxidised; hence in the later stages of electrolysis a solution of hydrogen peroxide is being electrolysed and undergoing its usual decomposition.

Influence of Factors affecting the Discharge.—Electrode distance. In Table 3 are shown the results of a series of experiments in which the distance of the anode from the electrolyte surface

TABLE 2. *Influence of volume, surface area, and stirring.*

	Fe^{++} oxidised (10^{-4} equiv.)				
Quantity of electricity (10^{-4} F)	Area, sq. cm. :	Stirred 10		Stirred 19	Unstirred 10
	Vol., ml. : 30	50	75	75	50
0·93	3·59	3·64	3·65	3·73	3·69
1·86	6·77	6·78	6·97	7·30	6·60
2·80	—	9·62	10·37	10·40	8·78
3·73	—	12·10	13·10	13·50	10·55

TABLE 3. *Influence of electrode distance.*

	Fe^{++} oxidised (10^{-4} equiv.)				
Quantity of electricity (10^{-4} F)	Distance of anode from solution surface, in cm.				
	0·15	0·38	0·77	1·30	1·95
0·93	3·87	3·77	3·64	3·77	3·82
1·86	7·75	7·07	6·78	6·92	7·07
2·80	10·47	10·17	9·62	9·95	10·07
3·50	12·25	12·10	11·60	11·85	11·95

was varied, standard conditions being otherwise employed. Apart from a trivial increase in yield when the anode is very close to the surface and the discharge is probably somewhat distorted, the electrode distance seems to have remarkably little influence.

Pressure. Experiments were carried out under the usual standard conditions at different pressures of nitrogen, and the results are summarised in Table 4. At the highest pressure the oxidation yields are somewhat increased, but apart from this the effect of pressure appears to be very slight.

TABLE 4. *Influence of pressure.*

	Fe^{++} oxidised (10^{-4} equiv.)			
Quantity of electricity (10^{-4} F)	Pressure of N_2 above the solution, in mm.			
	25	50	78	126
0·93	3·60	3·64	3·64	4·26
1·86	6·90	6·78	6·84	7·44
2·80	9·92	9·62	9·70	10·45
3·50	11·80	11·60	11·60	12·27

Influence of Factors affecting the Solution.—Temperature. The heat liberated in the glow-discharge electrolysis is so great that it is impossible to keep the temperature of the cell constant, but some experiments were carried out in which the average bulk temperature of the electrolyte was maintained at different values by varying the rate of flow of the cooling water; the results are given in Table 5. It is apparent that increase of temperature markedly increases the amount of oxidation corresponding to a given quantity of electricity.

Ferrous sulphate concentration. Preliminary experiments showed that variation of ferrous sulphate concentration had a significant effect upon the oxidation yield, and a comprehensive investigation of this factor was therefore made over the concentration range 0·005—0·935M-ferrous sulphate in 0·8N-sulphuric acid. With each solution, a graph of the amount of ferrous ion oxidised plotted against quantity of electricity passed was obtained, from which, by con-

structing tangents, the initial and final differential yields in equiv./faraday could be obtained. These are summarised in Table 6. The initial yields have been plotted against concentration in Fig. 3, and it may be noted that the initial yield increases rapidly at first with rise of ferrous sulphate concentration but ultimately approaches a value of about 7 equivs./faraday in the most concentrated solution. The final yield in each case (*i.e.*, the yield when the ferrous sul-

TABLE 5. *Influence of temperature.*

Quantity of electricity (10^{-4} F)	Fe^{++} oxidised (10^{-4} equiv.) Average temperature of electrolyte (approx.)		
	18°	27°	36°
0·93	3·64	4·26	5·28
1·40	5·20	6·00	7·96
1·86	6·78	7·62	9·81
2·33	8·24	9·26	12·05
2·80	9·62	10·83	—
3·27	10·90	12·19	—
3·73	12·10	—	—

TABLE 6. *Influence of ferrous sulphate concentration.*

$FeSO_4$, mole/l.	Differential yield, equiv. Fe^{++} oxidised/faraday		$FeSO_4$, mole/l.	Differential yield, equiv. Fe^{++} oxidised/faraday	
	Initial	Final		Initial	Final
0·005	3·1	1·6	0·10	5·8	2·5
0·01	3·4	1·8	0·15	6·2	2·4
0·015	3·6	2·4	0·20	6·4	2·6
0·025	4·2	2·5	0·30	6·8	2·7
0·05	5·0	2·5	0·935	7·0	—
0·075	5·4	2·6			

phate has been almost completely oxidised) increases initially with rise of concentration but then approaches a limiting value of *ca.* 2·5 equivs./faraday. The variation in yield during the course of any one electrolysis is apparently solely due to the decrease of ferrous-ion concentration as oxidation takes place; hence at any stage in one electrolysis the differential yield is the same as that obtained initially in a solution of corresponding ferrous-ion concentration. Thus the presence of ferric ions in the solution as oxidation proceeds appears to have very little effect. This was confirmed by comparing directly the results of the electrolysis of a mixture of ferrous and ferric sulphates with that of ferrous sulphate alone; no significant difference was observed.

The fact that the oxidation yield in all cases is much higher than the 1 equiv./faraday expected for electrolysis implies that some reduction product must also be formed in the anode compartment, and the most likely product appeared to be hydrogen arising from the water. To check this, a series of electrolyses were carried out with 0·075M-ferrous sulphate in 0·8N-sulphuric acid in which the gaseous products formed at the anode were estimated as well as the amount of oxidation in solution. The anode gas was found to contain considerable amounts of hydrogen together with small amounts of oxygen, and in Table 7 a comparison is made between the

TABLE 7. *Total products formed.*

Quantity of electricity (10^{-4} F)	Amounts of products (10^{-4} equiv.)				
	Fe^{++} oxidised	H_2	O_2	$H_2 - O_2$	Excess Fe^{++} oxidised
1·86	9·50	7·48	0·23	7·25	7·64
3·73	18·00	13·86	0·41	13·45	14·27
5·60	25·80	19·95	0·41	19·54	20·20
7·46	32·60	25·13	0·25	24·88	25·14
9·32	37·75	28·25	0·57	27·68	28·43

excess of oxidation in solution and the excess of hydrogen in the gas liberated. The last two columns agree well, showing that the excess of oxidation above that expected electrolytically is to be accounted for by simultaneous reduction of water to hydrogen.

Sulphuric acid concentration. The oxidation yield was found to increase as the concentration of sulphuric acid was raised. This is shown by the figures in Table 8 which refer to a 0·025M-ferrous sulphate solution and standard conditions.

Salt effects. In Part I it was noted that the anodic yield of hydrogen peroxide was increased by raising the concentration of the electrolyte in the medium used. This same tendency is apparent in the oxidation yield with ferrous sulphate solutions when inert salts are added to

the solution. A selection of results is given in Table 9. These were obtained with 0·025M-ferrous sulphate in 0·1N-sulphuric acid in the presence of various salts and are expressed as initial and final differential oxidation yields; for comparison the initial yields of hydrogen peroxide in the absence of ferrous sulphate are also given. It is seen that the oxidation yield

TABLE 8. *Influence of sulphuric acid concentration.*

H_2SO_4, equiv./l.	Differential yield, equiv. Fe^{++} oxidised/faraday		H_2SO_4, equiv./l.	Differential yield, equiv. Fe^{++} oxidised/faraday	
	Initial	Final		Initial	Final
0·02	3·4	1·6	0·80	4·2	2·5
0·10	3·6	1·8	3·6	4·8	2·5

with ferrous sulphate can be increased from 3·6 to 5·4 equivs./faraday by addition of inert salts, while the yield of hydrogen peroxide when ferrous sulphate is not present is raised from 1·1 to 2·3 equivs./faraday under comparable conditions. The effect appears to be largely independent of the chemical nature of the salt added and runs very roughly parallel to the ionic strength of the medium; it is noteworthy that the addition of a weak electrolyte such as boric acid did not influence the yields appreciably.

TABLE 9. *Influence of added salts.*

Salt added	Fe^{++} oxidised, equiv./faraday		H_2O_2 formed, equiv./faraday
	Initial	Final	Initial
None	3·6	1·8	1·1
0·02M-K_2SO_4	4·0	2·0	1·5
0·075M-K_2SO_4	4·5	2·5	1·7
0·10M-K_2SO_4	4·8	2·6	1·7
0·20M-K_2SO_4	5·4	2·6	2·3
0·10M-Na_2SO_4	4·8	2·6	1·7
0·10M-$(NH_4)_2SO_4$	4·8	2·6	1·7
0·075M-$MgSO_4$	4·4	2·4	1·5
0·075M-$ZnSO_4$	4·4	2·4	1·4
0·02M-$Al_2(SO_4)_3$	4·4	2·3	1·5
0·10M-$Al_2(SO_4)_3$	4·8	2·6	1·9

Oxygen. In the oxidation of ferrous sulphate solutions by ionising radiations the presence of dissolved oxygen often has a marked effect. In the present work it was found that pre-saturation of the solution with oxygen had no significant effect, probably because the solution is effectively degassed before electrolysis. If, however, the electrolysis was carried out in an atmosphere of oxygen instead of nitrogen, the oxidation yields were markedly increased, as the results in Table 10 show; replacing the nitrogen atmosphere by one of hydrogen did not

TABLE 10. *Influence of oxygen.*

Quantity of electricity (10^{-4} F)	Fe^{++} oxidised (10^{-4} equiv.) in atmosphere of :			Quantity of electricity (10^{-4} F)	Fe^{++} oxidised (10^{-4} equiv.) in atmosphere of :		
	N_2	O_2	H_2		N_2	O_2	H_2
0·47	1·90	2·97	—	2·33	8·20	11·73	—
0·93	3·64	5·54	3·58	2·56	8·84	12·40	—
1·40	5·30	7·98	—	2·80	9·62	—	10·10
1·86	6·78	10·05	6·95	3·73	12·10	—	12·30

influence the yields appreciably. The presence of oxygen raises the initial yield under standard conditions from 4·2 to 6·6 equivs./faraday, but the final yield remains unaffected at 2·5 equivs./faraday. The same tendency was found with ferrous sulphate solutions over the whole range of concentrations, and with 0·78M-ferrous sulphate in 0·8N-sulphuric acid the very high initial yield of 11·6 equivs./faraday was found as compared with a maximum yield of about 7 equivs./faraday observed in electrolysis under nitrogen. It is noteworthy that no oxidation of ferrous sulphate solution was brought about by passing a discharge between platinum electrodes just above the liquid surface in an oxygen atmosphere; this suggests that the effect of oxygen in the glow-discharge electrolysis must be a fundamental one.

DISCUSSION

In Part I (*loc. cit.*), arguments were presented which suggested that with a glow-discharge anode the current is conveyed across the gas–liquid interface by positive gaseous ions derived from water vapour; these, it was supposed, are driven into the liquid from the gas phase under the high potential gradient which exists near the cathode (*i.e.*, liquid) surface

and are subsequently discharged. In these circumstances in addition to any purely electrolytic action it is possible that entry of positive gaseous ions into the solution may bring about dissociation of water molecules in the general way now attributed to ionising radiations of many types (cf. Dainton, *Ann. Reports*, 1948, **45**, 5). In the earlier work the yields of hydrogen peroxide obtained were not usually very much greater than 1 equiv. per faraday, and it was possible to regard this product as arising mainly by electrolytic action although the possibility of some direct dissociation of water molecules was not excluded. The present investigation of the oxidation of ferrous sulphate shows that oxidation yields vastly in excess of that expected from electrolysis occur accompanied by evolution of hydrogen from the solution, and it is at once apparent that in this case electrolysis is of minor importance and the oxidation occurs mainly *via* the dissociation of water molecules. Quantity of electricity is still the experimental factor of prime importance, but it now serves to measure the number of charged particles which have entered the solution, and the chemical effects they produce are much greater than is to be expected simply by a transference of charge.

The primary result of the passage of current across the gas–water interface can be represented quite generally in conventional terms as follows :

Charge transference $H_2O - e \longrightarrow H_2O^+ \longrightarrow OH + H^+$ . . . . . (*a*)

Dissociation $H_2O \longrightarrow H_2O^+ + e \longrightarrow OH + H$ . . . . . (*b*)

Thus the oxidising species arising either from electrolysis or from dissociation will be the same, but the electrolytic reaction (*a*) yields only 1 equiv. of OH per faraday, while the dissociation reaction (*b*) may produce several equivalents of OH per faraday, depending upon the energy available, but these will be accompanied necessarily by a corresponding number of equivalents of hydrogen. In the absence of a depolariser, dimerisation of the OH radicals to give hydrogen peroxide may then occur in the way previously discussed (Part I). In the presence of a ferrous salt, the ferrous ion may be oxidised by the OH radical either directly

$$Fe^{++} + OH \longrightarrow Fe^{+++} + OH^- \quad . . . . . (c)$$

or *via* the formation of hydrogen peroxide

$$2OH \longrightarrow H_2O_2 \quad . . . . . (d)$$

followed by $2Fe^{++} + H_2O_2 \longrightarrow 2Fe^{+++} + 2OH^-$

and these reactions will compete with the back reaction

$$OH + H \longrightarrow H_2O \quad . . . . . (e)$$

Thus if n equivalents of OH are formed per faraday by the dissociation reaction (*b*), and if v_1, v_2, and v_3 are the velocities of reactions (*c*), (*d*), and (*e*) in the stationary state, then the oxidation yield (G) in equivalents per faraday will be given by the equation

$$G = 1 + n\frac{v_1 + v_2}{v_1 + v_2 + v_3} \quad . . . . . (1)$$

The velocities being expressed in terms of the concentrations of the reacting species, this becomes

$$G = 1 + n\frac{k_1[OH][Fe^{++}] + k_2[OH]^2}{k_1[OH][Fe^{++}] + k_2[OH]^2 + k_3[OH][H]} \quad . . . . . (2)$$

which simplifies to

$$G = 1 + n\frac{[Fe^{++}] + k_2[OH]/k_1}{[Fe^{++}] + k_2[OH]/k_1 + k_3[H]/k_1} \quad . . . . . (3)$$

Under a given set of experimental conditions it is reasonable to suppose that in the stationary state [OH] and [H] are constant and the equation may then be written

$$G = 1 + n\frac{[Fe^{++}] + A}{[Fe^{++}] + A + B} \quad . . . . . (4)$$

where A and B are constants. The numerical values of A, B, and n can be determined by reference to the experimental data in the following way. On rearranging equation (4) and inverting it, we have

$$\frac{1}{G - 1} = \frac{1}{n} \cdot \frac{B}{A + [Fe^{++}]} + \frac{1}{n} \quad . . . . . (5)$$

At substantial concentrations of ferrous sulphate $A + [Fe^{++}] \simeq [Fe^{++}]$ and hence the plot of $1/(G - 1)$ against $1/[Fe^{++}]$ should be a straight line of slope B/n and intercept $1/n$. Furthermore, at very low ferrous-ion concentrations the oxidation yield should be constant and have the value

$$G = 1 + nA/(A + B) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

from which A can be found. On treating the data in Table 6 in this way, we obtain the values $n = 6{\cdot}2$, $B = 0{\cdot}030$, and $A = 0{\cdot}0096$, and hence the dependence of the initial differential yield upon the ferrous-ion concentration should be given by the equation

$$G = 1 + 6{\cdot}2[(Fe^{++}] + 0{\cdot}0096)/([Fe^{++}] + 0{\cdot}0396) \quad . \quad . \quad . \quad . \quad . \quad (7)$$

This relation has been tested by calculating G for different ferrous sulphate concentrations and in Table 11 these calculated values are compared with those found experimentally.

TABLE 11. *Experimental and calculated oxidation yields.*

$FeSO_4$, mole/l.	0·005	0·010	0·015	0·025	0·05	0·075	0·10	0·15	0·20	0·30	0·935
$G_{expti.}$	3·1	3·4	3·6	4·2	5·0	5·4	5·8	6·2	6·4	6·8	7·0
$G_{calc.}$	3·0	3·4	3·8	4·3	5·1	5·6	5·9	6·2	6·4	6·7	7·0

The agreement between the experimental and calculated values is very satisfactory, which suggests that the method of deriving the equation is sound in principle. It is noteworthy that according to equation (7) the oxidation yield is practically independent of ferrous sulphate concentration at concentrations below 10^{-3} mole/l.; in the oxidation of ferrous sulphate by α-rays a similar change to a concentration-independent region is found at low concentrations (cf. Nurnberger, *J. Phys. Chem.*, 1934, **38**, 47).

In the reaction scheme which has been postulated, no reduction of the ferric salt produced by the hydrogen formed in the dissociation of water has been suggested. All the experimental evidence in the present work indicates that no reduction of this type takes place. Thus the oxidation of the ferrous salt proceeds to completion independently of the concentration of ferric ions present, and even when a glow-discharge cathode was used with a ferric sulphate solution very little reduction could be brought about. This absence of reducing power in a system in which the existence of hydrogen atoms is postulated has frequently been noted in the radiation field, and much ingenuity has been directed to explaining it (see, *e.g.*, Haissinsky, *Discuss. Faraday Soc.*, 1952, **12**, 133).

Estimates of the cathode fall of potential have been made in the present work from observations on the variation of anode–cathode voltage with anode–surface distance, the ohmic drop in the solution being negligible. These indicate that it is approximately 470 v, and it appears to be independent of current, pressure, and nature of the solution, and to be confined to a layer less than 1 mm. thick near the liquid surface. Thus the energy of the positive ions reaching the solution is independent of most experimental variables and hence n will be constant. Since n has normally a value of 6·2, it follows that the maximum energy required on the present scheme to form an ion-pair cannot exceed about 76 ev; the actual energy may be much less than this, since some will undoubtedly be lost in collision processes. If n is constant, it follows from equation (3) that, apart from the ferrous-ion concentration, the oxidation yield will only be affected by variation in the stationary concentrations of the radicals or in the velocity coefficients. The concentrations of the radicals would be expected to be directly connected with the current density in the reaction zone, and hence measurements have been made of the area of the glow-spot in the water surface under different experimental conditions. These show that the current density (I) is independent of the actual current used (the spot expanding proportionately as the current is increased) and of the nature of the electrolyte, but varies as the square root of the pressure (p), the average of a large number of determinations giving $Ip^{-\frac{1}{2}} = 0{\cdot}018$ A/sq. cm./mm.$^{\frac{1}{2}}$, and is only slightly affected by change in the anode–surface distance. The yield should thus be independent of current and practically independent of pressure and anode–surface distance, as was found experimentally. It should be emphasised that all the reactions considered are regarded as being confined to a localised reaction zone beneath the glow-spot in the liquid surface.

Increase of temperature has been found markedly to increase the oxidation yield with

the stock ferrous sulphate electrolyte, and it also increases the yield of hydrogen peroxide when no oxidisable substance is present (see Part I). It was found by experiments with concentrated ferrous sulphate solutions that there is an increase in n with rise of temperature; by substituting the values obtained in equation (7), however, it appears that this alone is insufficient to account for the increase of yield observed at lower concentrations. This would imply, therefore, that the overall velocities of the oxidation reactions are increased by rise of temperature; this could arise by there being an energy of activation both for the interaction of the OH radical with the ferrous ion [reaction (*c*)] and for the dimerisation reaction (*d*), or possibly by the acceleration of diffusion processes in the reaction zone. It is not yet feasible to distinguish clearly between these possibilities.

The marked effect of oxygen in increasing the initial yield in the oxidation of ferrous sulphate can be simply explained on the supposition, frequently made in radiation chemistry, that oxygen reacts with hydrogen atoms as follows :

$$H + O_2 \longrightarrow HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (f)$$

The HO_2 radicals produced might then themselves bring about oxidation by an initial reaction of the type

$$\left.\begin{array}{rl} & Fe^{++} + HO_2 \longrightarrow Fe^{+++} + HO_2^- \\ \text{followed by} & 2Fe^{++} + HO_2^- + H^+ \longrightarrow 2Fe^{+++} + 2OH^- \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (g)$$

Thus there would be an increase in the number of oxidising radicals formed and a decrease in the concentration of hydrogen atoms leading to a reduction in the speed of the back reaction (*e*). In practice, the experimental results show that n in equation (4) is raised from 6·2 to 11·1 by the presence of oxygen, and since the energy expended in the discharge remains the same, this can only be attributed to the formation of new oxidising species by chemical reaction as suggested.

The theory which has been outlined so far has assumed that the OH radical is in general the primary effective oxidising agent, and it has provided a plausible explanation of most of the experimental observations. The very marked effect of inert salts in raising the oxidation yields with ferrous sulphate, and in the formation of hydrogen peroxide, receives no obvious interpretation on this theory, however, and it suggests another possibility. The effect, which has also been observed in radiation chemistry, is of so general a nature that it appears to be unmistakably due to the change of ionic environment on addition of an electrolyte, *i.e.*, to arise by a primary salt effect on the velocities of the reactions involved. This would imply that charged species are concerned in the reactions. Now it has been suggested that H_2O^+ is a precursor of the OH radical, and this might then react directly with the ferrous ion

$$Fe^{++} + H_2O^+ \longrightarrow Fe^{+++} + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (h)$$

while the back reaction would be

$$\left.\begin{array}{rl} & H_2O^+ + e \longrightarrow H_2O \\ \text{or} & H_2O^+ + H_2O^- \longrightarrow 2H_2O \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

Reaction (*h*) would then be accelerated and reaction (*i*) retarded by addition of electrolytes, giving the enhanced oxidation yields as found; in the absence of ferrous sulphate, the retardation of the back reaction would lead to an increased yield of hydrogen peroxide as observed. A further attractive feature of this scheme is that in acid solution there is a possibility of the reaction of H_2O^- with a hydrogen ion leading to the direct elimination of molecular hydrogen rather than the formation of hydrogen atoms, thus :

$$H_2O^- + H^+ \longrightarrow H_2 + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (j)$$

This would account for the absence of reducing properties in the solution, each initial act of dissociation leading to the formation of 2 oxidising radicals and 1 molecule of hydrogen. In the presence of oxygen a possible reaction is

$$H_2O^- + O_2 \longrightarrow HO_2 + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (k)$$

and in view of the stoicheiometry of reaction (*g*) where one HO_2 radical oxidises 3 ferrous ions, the value of n should be increased.

The postulation of these ionic reactions in addition to or in place of the free-radical

reactions of the more conventional scheme would not change fundamentally the previous treatment of the system, but it appears to satisfy certain requirements where the free-radical reaction scheme is inadequate. It must, however, be noted that the participation of H_2O^+ and H_2O^- in the reactions is not in conformity with the generally accepted view of the instability of these ions in solution, and while the hypothesis advanced has many attractive features it must be regarded as speculative.

DEPARTMENT OF PHYSICAL AND INORGANIC CHEMISTRY,
UNIVERSITY OF LIVERPOOL.

[*Received, July 7th,* 1953.]

Electron Transfer in Alkali Metal–Hydrocarbon Complexes.

By W. A. HOLMES-WALKER and A. R. UBBELOHDE.

[Reprint Order No. 4637.]

Solid complexes formed between lithium, sodium, or potassium and anthracene have been isolated in the solvent-free condition, and some of their physicochemical properties have been investigated.

By various procedures, the ratio of alkali metal (M) to anthracene (An) can be varied roughly within the range M_1An and M_2An. On formation of any of these complexes considerable electrostriction takes place, and the large "aromatic diamagnetism" is replaced by comparatively large paramagnetism, whose dependence on temperature and composition is reported. The complexes show semi-conductor behaviour with activation energy ranging from 1·36 to 0·76 ev.

From these and other properties it is suggested that the complexes are formed by a non-stoicheiometric electron transfer between the alkali-metal atoms and the hydrocarbon molecules.

THE addition of potassium or bromine to graphite results in enhanced metallic properties (McDonnell, Pink, and Ubbelohde, *J.*, 1951, 191). From this it was inferred that layers of fused aromatic nuclei in graphite are able both to accept electrons from potassium atoms, and donate them to bromine atoms, yielding in both cases pseudo-metallic structures.

The present research was designed as an investigation of the bonding between alkali-metal atoms and networks of fused aromatic nuclei smaller than in graphite. Methods are described (*a*) of preparing addition compounds of anthracene with lithium, sodium, or potassium in various solvents, and of isolating and handling the solvent-free solids, and (*b*) of varying the composition of the sodium compounds in the range $Na_{1\cdot08}An$ to $Na_{2\cdot12}An$.

From measurements of electrical conductance on these solids, they appear to form a class of semi-conductors with positive temperature coefficient of conductance. This conductance is many times that of the parent hydrocarbon, and varies with the alkali metal and composition of the complex.

Magnetic measurements with sodium anthracene show that the diamagnetism due to the π-electrons of anthracene is destroyed. Instead, the complex is increasingly paramagnetic as the mole-fraction of the metal becomes greater. A tentative interpretation is that electron-transfer bonds (cf. McDonnell, Pink, and Ubbelohde, *loc. cit.*) are formed in the solid between the alkali-metal atoms and the hydrocarbon molecules. The solids described below have electronic analogies with solutions of alkali metals in liquid ammonia.

EXPERIMENTAL

Generally the addition complexes were formed by direct action between the alkali metal and the hydrocarbon, one of the solvents described below being used, in systems protected against access of oxygen or moisture. Access of direct sunlight was also prevented as far as possible by using black cloth wrappings on the vessel (Reid and Ubbelohde, *J.*, 1948, 1597). Special methods of manipulation described below permitted the filtration of excess of solvent from the solids, and the removal of any solvent of crystallisation. The dry solids were then examined

for various physicochemical properties, by methods previously described (McDonnell, Pink, and Ubbelohde, *loc. cit.*) except where otherwise stated.

Preliminary experiments have also been carried out on the direct synthesis of the complexes by bombarding the warm crystals of the hydrocarbon with atoms of the alkali metal. These experiments showed promising results, but are not further detailed.

Materials.—Nitrogen. Nitrogen (British Oxygen Co.) was carefully freed from oxygen by passage over copper turnings at 500° and dried by passage through a "Birlec Lab Lectrodryer." All future references to nitrogen imply gas purified as above.

Anthracene. This had setting point 215° as obtained "pure" from the Deutsche Gesellschaft fur Teerverwertung. Though other hydrocarbons form addition compounds more readily, it was important to lessen the burden of exploratory work by selecting an easily available substance.

Alkali metals. Sodium was cleaned by cutting away most of the oxide in air, transferring the metal to a tube continuously swept out by nitrogen, and then again cutting shavings from all faces of the cubes. Metal thus obtained remained brightly reflecting for at least 2 min. after cutting, but then slowly lost its polish, possibly owing to surface recrystallisation. It started to react immediately when added to anthracene suspended in a solvent.

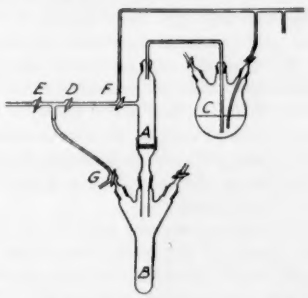


FIG. 1. *Apparatus for preparing potassium anthracene.*

Lithium (B.D.H. 98% pure) was freed from mineral oil with filter-paper, and then treated in the same way as sodium.

Potassium (B.D.H. "pure") was scraped as free as possible from oxide, filtered through a glass capillary *in vacuo*, and then distilled with the precautions previously described (*idem, loc. cit.*).

Solvents. All solvents were rigorously dried and purified unless otherwise specified. Diethyl ether was purified as described by Mackle and Ubbelohde (*J.*, 1948, 1161). Dimethoxyethane, recommended as a solvent because of its low C : O ratio (Scott, Walker, and Hansley, *J. Amer. Chem. Soc.*, 1936, **58**, 2442; Jeanes and Adams, *ibid.*, 1937, **59**, 2608), was not conveniently available.

Particularly where a higher temperature was advantageous, some preparations were achieved with "AnalaR" dioxan refluxed over sodium and distilled off the metal in the range 100—101·5°. Generally, however, preparations with diethyl ether were more straightforward.

Preparation of Complexes.—Previous methods were not concerned with preparation of the complexes completely free from solvent (Schlenk, *Ber.*, 1914, **47**, 473; Scott *et al.*, *loc. cit.*). After some investigation two useful methods were developed for preparing the solids in a solvent-free condition.

The apparatus (Fig. 1) was suitable for comparatively involatile solvents such as dioxan. It was first swept out with nitrogen as far as tap *E*. Gas flow was adjusted by the rate of bubbling through the solvent in the three-necked flask *C*. A weighed amount of anthracene (about 2 g.) and about 100 ml. of dioxan were then placed in the sintered-filter vessel *A*. An upward stream of nitrogen served to prevent any filtration at this stage, and also prevented entry of air at the top of *A*. Excess of alkali metal M, about 20% over the amount required for the complex M_2An, was added to the mixture in *A*, counter-currents of nitrogen being used to protect the metal. A heater was used to raise the temperature and increase the solubility of the anthracene in dioxan. However carefully the dioxan had been purified, at first a transparent skin formed on the metal. Possibly this was due to the transformation to acetal (Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier Publishing Co., Inc., 1950, p. 502) with concurrent formation of metal oxide. This skin slowed

down the reaction, but above the m. p. globules of metal burst through. As the reaction proceeded slowly, a strong blue colour developed round the metal. When the b. p. of the solvent was reached, the whole solution became an intense royal-blue, which gradually changed to the deep green described by Scott *et al.* (*loc. cit.*). After about 1 hr., during which the nitrogen pressure was controlled by a mercury U-tube gauge, the hot solution was filtered into *B* by suitable operation of the taps *D*, *E*, *F*, and *G*. All insoluble matter remained on the filter. The hot, deep green filtrate on cooling deposited dark green crystals. However, these tended to become yellow if kept in dioxan for long periods. To obviate this, the dioxan was sucked off. Any dioxan adhering to the crystals was replaced by successive decantations with diethyl ether. The potassium anthracene complex was dark green, and became bluer as the dioxan was replaced by ether. The solvent-free complex was grey. The above method was used for the potassium compound, where the higher temperature was an advantage. However, in view of the slow interaction of the complex with dioxan, the following method was developed for lithium and sodium compounds.

Anthracene (2—3 g.) was added to diethyl ether (200 ml.) under nitrogen in a three-necked flask. On introduction of an excess of lithium or sodium protected by nitrogen, and mechanical stirring, the reaction started immediately. Within 10 min. the whole solution was deeply coloured—purple in the case of lithium, and indigo with sodium. After some 48 hr. or so the stirring was stopped, and the ethereal layer siphoned off. The coloured solid was washed by decantation with several portions of ether. When the remaining ether was removed by increasing the flow of nitrogen, the deep colour—purple with lithium, and blue-green with sodium—remained until all traces of ether were removed. The resulting homogeneous powder was yellow for lithium, and a red-pink for sodium. Any pieces of metal which had not reacted could then be picked out, as they remained bright.

Potassium was difficult to be made to react under ether. Ampoules of the redistilled metal had to be broken in the flask, and any exposed metal rapidly became covered with blue product. The reaction then stopped.

Densities.—In connection with the measurements of magnetic properties, rough determinations were made of the bulk densities in the Gouy tubes. Results are recorded in Table 1. Measurement of the true density was made on a sample of sodium anthracene under nitrogen, a conventional pycnometer being used. Purified Nujol, used as the fluid, was dried by keeping it at 120° for 12 hr. while nitrogen was bubbled through it. The measured density of sodium anthracene $Na_{1\cdot70}An$ at 20° was 1·33 g./c.c. Similarly the density at 20° of $Na_{1\cdot60}An(Et_2O)_{0\cdot30}$ was 1·26 g./c.c.

Analysis of Products.—Direct action of water or dilute acids on the solids produced tars. This suggests the intermediate liberation of free radicals which polymerise. After some investigation two methods were found to be satisfactory.

(1) A sealed ampoule containing the solid was weighed and broken into about 100 ml. of 50% aqueous methyl alcohol. A known volume of standard hydrochloric acid was added. After the liberated hydrocarbon had been filtered off and washed, the solution was made up to a known volume and titrated against standard sodium hydroxide solution, with bromocresol-green as indicator. The amount of acid neutralised was proportional to the sodium present in the compound. The hydrocarbon recovered melted at 110° and appeared to be dihydro-anthracene. This analysis was quite straightforward provided small amounts of complex were used. With amounts greater than 0·5 g., intermediate products were obtained which prevented a true end-point in the titration.

(2) A weighed ampoule containing the solid complex was broken into benzene. The sodium was then removed by washing with water, and weighed as sulphate. Finally, the hydrocarbon produced in the benzene layer was isolated; from the solid with approximate composition Na_2An it was identified as dihydroanthracene.

Determination of retained ether. Following an unpublished method developed by Nichol and Ubbelohde, ether is oxidised in the cold on being kept with an excess of strongly acidified dichromate solution. Unchanged dichromate is determined by back-titration against standard ferrous ammonium sulphate solution.

Ether was removed from a weighed amount of the highly coloured complex, which retains it only moderately, by passing a stream of nitrogen, and was collected by passing the gas through a liquid-air trap. The contents of the trap were treated with 20 ml. of 0·5N-potassium dichromate solution previously acidified with 20 ml. of concentrated sulphuric acid. Separate tests showed that after 20 min. the ether was quantitatively oxidised to acetic acid. The unchanged dichromate was estimated by back-titration against 0·5N-ferrous ammonium sulphate

solution, *N*-phenylanthranilic acid being used as indicator. The composition established by analysis (see Table 1) suggests that part of the ether was lost during handling. The dark, highly coloured powders studied may have consisted of a mixture of solvated complex and solvent-free crystals. Co-ordination of the solvent appears to play a part in the structure of the highly coloured compounds formed in electron-donor solvents, in view of the change in colour observed when the last traces of solvent are removed. This possibility was left for future study, since, as explained above, the present paper deals primarily with the solvent-free solids.

Magnetic Measurements.—Susceptibility measurements were made at 90° K and 288° K by the Gouy method already described (McDonnell, Pink, and Ubbelohde, *loc. cit.*). The field strength used was approx. 3600 gauss. Results are recorded in Table 1.

TABLE 1. *Magnetic susceptibilities* (*c.g.s. units* × 10^6) (χ_m is based on 1 mole of anthracene throughout).

Substance	90° K		288° K		Bulk density (g./c.c.)
	χ_s	χ_m	χ_s	χ_m	
Anthracene (An)	—	—	−0·718	−127·9	0·389
$Na_{1·42}An$	+0·502	+105·6	+0·183	+ 38·4	0·360
$Na_{1·70}An$	+0·510	+110·7	+0·082	+ 17·8	0·403
$Na_{1·96}An$	—	—	+0·338	+ 75·4	0·408
$Na_{2·02}An$	+3·86	+864·6	+3·25	+728·1	0·300
$Na_{2·12}An$	—	—	(+1·22)	(+262·0)	0·302
$Na_{1·60}An(Et_2O)_{0·30}$	(+0)	(±0)	+0·255	+ 60·3	0·398

Notes. (1) The results for $Na_{2·12}An$ are less reliable, owing to the smaller quantities available. (2) The values for $Na_{1·60}An(Et_2O)_{0·30}$ are within experimental error approximately zero at 90° K. Fluctuations were obtained in successive readings.

Electrical Conductance (σ) *of Solids.*—The apparatus used (Fig. 2) was a modification of that used by McDonnell, Pink, and Ubbelohde (*loc. cit.*). Electrodes were of copper. All measurements were made under nitrogen, and the solid complex was introduced into the cell chamber by rotation at the greased joints *C* and *E*. Temperature variation was effected by means of a small air-furnace wound on a Pyrex tube lagged with asbestos, and fitted with baffle-screens to eliminate temperature fluctuations; 220 volts D.C. was applied across the electrodes, and the resulting currents were measured with a sensitive galvanometer and optical system, giving resistance measurements up to 2 × 10^{13} ohm. A typical plot of resistance–column height is given in Fig. 3. The curve is not a straight line, possibly owing to very slight irregularities in column packing. Fig. 4 illustrates plots of log $_{10}\sigma$ against $1/T$. In two cases at least this representation of the plot by a single straight line is inadequate; these are shown in Fig. 5. The electrical parameters are summarised in Table 2.

TABLE 2. *Electrical conductance of anthracene and its complexes.*

Substance	Conductance (ohm^{-1} cm.$^{-1}$), $10^{12}\sigma$	Concn. of metal, x in M_xAn	$10^5\sigma_0$ (ohm^{-1} cm.$^{-1}$)	E (ev)
Li anthracene	7·73	1·16	335	1·32
	4·54	1·16	907	1·36
K anthracene	6·38	1·18	445	1·10
	5·29	1·18	1,773	1·13
	14·2	1·18	473	1·07
Na anthracene	45·3	1·08	288,400	1·20
	341	1·42	513,300	1·16
	714	1·70	10·3	0·88
	1885	2·02	0·191	0·76
	320	2·12	$3·2 \times 10^{-5}$	0·58
	5040		66·0	0·99
$Na_{1·60}An(Et_2O)_{0·30}$	16·1	1·60	$2·56 \times 10^{-9}$	0·13
	41·7		4,055	1·23

Notes. (1) Values of E and σ_0 are calculated from the expression $\sigma = \sigma_0 e^{-E/kT}$, where σ is the specific conductance at temperature T. (2) The values of σ quoted are at 293° K for all substances except Li anthracene which is calculated for 353° K. (3) The values for E are the mean values of the results obtained by calculation of lines of closest fit (cf. Figs. 4 and 5).

Where the log σ–$1/T$ plots break up roughly into two straight lines, two values are given.

Electrical Conductance of Solutions.—Scott *et al.* (*loc. cit.*) reported that the coloured solutions of sodium naphthalene in dimethoxyethane were "highly conducting," but it appears possible that this conductance was due, at least in part, to sodium hydroxide formed by traces of water in the systems described. When the solvent-free solids were added to solvents such as dioxan,

diethyl ether, anisole, or benzene, the dark solutions were not re-formed, but instead a brown suspension was obtained. Thus the change from highly coloured solids to the solvent-free solids on removing all the retained solvent is not readily reversible. Mercury had no visible effect on the coloured solutions or the solvent-free complexes, unlike its effect with more reactive complexes (Schlenk, *loc. cit.*).

An attempt was made to measure the conductance of solutions of sodium anthracene. A pair of platinum electrodes, each 0·6 cm. × 1·3 cm. and 0·2 cm. apart, were used at temperatures from 0° up to 100°, at which the concentration of dissolved material was about 3 g. per 100 ml. of solvent. The specific resistance was greater than 10^{12} ohm cm. in both ether and

FIG. 2. *Electrical conductance apparatus.*

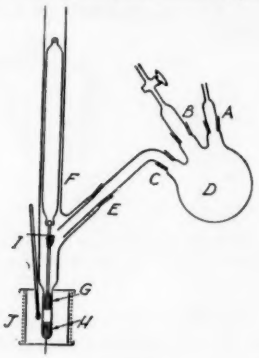


FIG. 3. *Electrical resistance of sodium anthracene.*

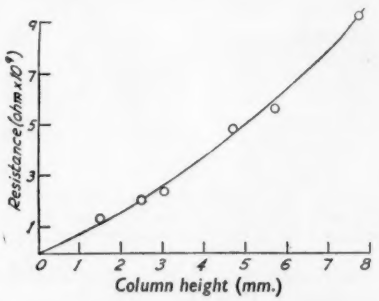


FIG. 4. *Logarithmic plot of specific conductance.*

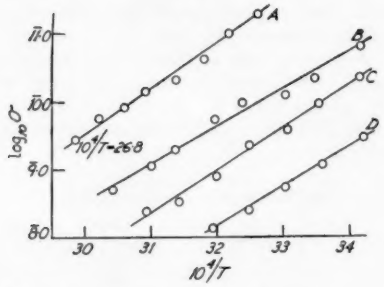
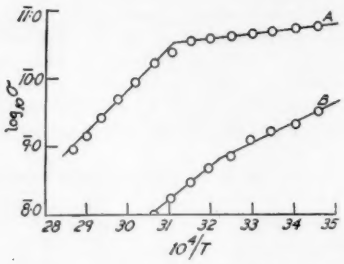


FIG. 5. *Logarithmic plot of specific conductance.*



Curve A * *represents values for* $Li_{1\cdot16}An$.
„ *B* „ „ $K_{1\cdot18}An$.
„ *C* „ „ $Na_{1\cdot08}An$.
„ *D* „ „ $Na_{1\cdot42}An$.

Curve A represents values for $Na_{1\cdot60}An(Et_2O)_{0\cdot30}$.
„ *B* „ „ $Na_{2\cdot12}An$.

* Note shift of zero on the *x*-axis for this curve.

dioxan solutions of the dark solvated or lighter coloured unsolvated complexes. However, in pure dry anisole, prepared by the general methods described for ether, a new phenomenon was observed. The specific resistance of the solvent was greater than 10^{12} ohm cm. When excess of the solvent-free sodium anthracene $Na_{1\cdot70}An$ was added, the resistance remained high, but the suspended particles showed a tendency to migrate towards the anode. On gradual rise of the temperature to the b. p. of anisole, the resistance gradually decreased to about 4×10^{10} ohm cm. The colour of the suspended solid deepened from brown to almost black, and now it tended to cluster round the cathode. By degrees, " bridges " were formed across to the anode. When the current was switched off, the solid fell away, to repeat the phenomenon as soon as the current was switched on again. On cooling, the resistance slowly rose. After a day or so the brown colour was restored to the solid, which was once more attracted to the anode. Samples taken from the supernatant anisole solution showed differential extraction of

anthracene from the complex, as described below. Extraction of anthracene by the anisole was also shown by the marked fluorescence of the clear solution at the higher temperature.

Physicochemical Stability of the Complexes.—Stability towards air or water varied considerably with the amount of solvent present. The ethereal sludge containing the deeply coloured solid decomposed rapidly. Even when all the easily removed ether was driven off, the highly coloured complexes reacted violently with air or water. When all traces of retained solvent had been removed, decomposition of the much less highly coloured unsolvated solids was rapid but less violent.

The physicochemical stability of the solvent-free sodium complexes was tested more extensively in two further ways. When heated in a high vacuum the compounds remained unchanged up to 60°. At about 80° the solid began to darken, and a white sublimate appeared. Mixed m. p. tests confirmed that this sublimate was anthracene. Slight further darkening occurred up to 500°. At 550° the residue rapidly shrivelled and blackened.

Other samples of the solvent-free sodium complexes were washed on a sintered-glass filter under nitrogen with successive aliquot portions of a solvent. Both benzene and ether were used, as shown in Table 3. When the solutions were analysed, as above, the results showed that the solid initially lost more anthracene than sodium until it reached a limiting composition approximately corresponding to Na_2An. The amount of sodium recovered from each washing remained constant for a particular solvent, and was greatly increased if the solvent was not perfectly dry.

TABLE 3. *Analysis of fractions after sodium anthracene had been washed with successive aliquot portions of solvent.*

Solvent	Component	Millimoles of substance per 10 ml. of solvent in washing no. : 1	2	3	4	5	6
Benzene	Anthracene	0·124	0·018	0·017	0·018	0·018	0·017
	Sodium	0·028	0·035	0·035	0·035	0·032	0·035
Ether	Anthracene	0·140	0·020	0·017	0·018	0·016	0·017
	Sodium	0·035	0·034	0·035	0·032	0·032	0·032

X-*Ray Examination of Sodium Anthracene.*—Very thin Pyrex specimen tubes filled and sealed off under nitrogen being used, *X*-ray photographs were taken by means of an Ubbelohde multiple-exposure camera with Cu radiation and Ni filter. Pure anthracene and several specimens of sodium anthracene, with compositions ranging from $Na_{1\cdot40}An$ to $Na_{1\cdot96}An$, were examined. With increasing mole-fractions of sodium, there was a gradual replacement of some of the lines due to anthracene, and a strengthening of others, as if solid solution was taking place. Further analysis awaits detailed comparisons with the corresponding potassium complexes and, if possible, study on single crystals.

DISCUSSION

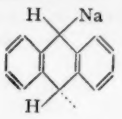
Electro-striction on Complex Formation.—From the density measurements, the volume of $Na_{1\cdot70}An$ containing 1 mole of anthracene is 163·4 c.c. This compares with 155·0 c.c. per mole of pure anthracene, and 40·3 c.c. corresponding with the amount of pure metallic sodium present. As in the case of potassium graphite, the volume shrinkage, $155\cdot0 + 40\cdot3 - 163\cdot4 = 31\cdot9$ c.c., is much too large to be accounted for in terms of isolated atoms of sodium dispersed in some way in the anthracene without any strong electron interaction. Some kind of electrostriction is indicated. Suppose the change in volume of anthracene after electron transfer to form An^- is Δ c.c. per mole. If a close-packed ionic compound $(Na^+)_2\ An^-$ is formed, the molar volume of Na^+ can be calculated to be 3·67 c.c. from the equation $V = 1\cdot70N(4/3\pi r^3)$, where N is Avogadro's number, and $r = 0\cdot95$ Å is the radius of the Na^+ ion. The volume of such a complex would be $155\cdot0 + \Delta + 3\cdot67$ c.c. Though the increment Δ cannot yet be assessed acurately, it is likely to be a small positive value. The near correspondence between $158\cdot67 + \Delta$ c.c. and the observed 163·4 c.c. suggests that the structure may be nearly but not wholly ionic.

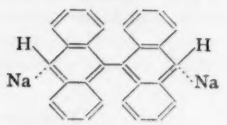
A similar calculation can also be made for the results on the complex $Na_{1\cdot60}An(Et_2O)_{0\cdot30}$. This gives a volume of 188·1 c.c. containing 1 mole of anthracene. Allowing 30 c.c. for the 0·30 mole of ether, the net contraction in this case is thus $155\cdot0 + 37\cdot9 + 30 - 188\cdot1 = 34\cdot8$ c.c. This contraction is even larger than for the solvent-free complex, suggesting that electrostriction may be greater in the solvated complex.

Marked electrostriction would be expected if every atom of sodium in the crystal Na_2An transferred one electron to the neighbouring anthracene molecule, thus forming a truly ionic compound $(Na^+)_2\ An^=$, similar, for example, to Na_2S. Reasons for supposing that the structure is not simply salt-like are discussed below. The model at present envisaged consists of a crystal in which different fractions of the lattice sites are occupied by An molecules carrying charges -2, -1, and 0. The neighbouring sodium atoms carry charges $+1$ or 0, so as to preserve substantial electrostatic neutrality over any plurality of sites. This model is equivalent to saying that there is transfer of electrons in the crystal on a statistical basis, but not 100% stoicheiometric transfer. The electrical conductivity results from movements of electrons in the crystal, as in Pauling's theory of metals. However, the fact that the conductivity shows marked activation energy indicates that, unlike the position in true metals, there must be appreciable potential barriers opposing conduction in our solids.

Magnetic Properties.—Results show that the large " aromatic " diamagnetism of the anthracene is replaced by paramagnetism. This behaviour is again parallel with that of potassium graphite, except that with anthracene complexes the paramagnetic susceptibility generally increases with falling temperature. Temperature dependence is particularly marked for solids whose overall analysis shows a ratio of sodium to anthracene well below 2 : 1.

One explanation could be that the solid complexes include some " free-radical " monosodium anthracene (I). The formation of such a radical in solution is suggested by Schlenk (*loc. cit.*) and is also indicated by the production of the bright blue colour in the early stages of the dioxan preparations which later gave place to the dark green colour. With methods of preparation at present available it cannot be decided whether such a free radical is in solid solution, or whether it is present as a pure crystalline component in a mixture of crystals. The hydrocarbon recovered from chemical analysis, and from elutriating the solids with excess of solvent, indicates that no appreciable amounts of dianthracene derivatives (II) such as are formed in the solid (cf. Schlenk and Bergmann, *Annalen*, 1928, **463**, 1). Alternatively, if they are formed, coupling between mono-radicals in the solid must be fairly labile and easily dissociated by excess of sodium atoms such as would be left on extraction of some of the anthracene.

(I) 



(II)

Because of this uncertainty in the distribution of sodium atoms and free valencies in the solid, the magnetic and electrical properties quoted for the solids should for the present be regarded as illustrative of the order of magnitude encountered in the different preparations. Thus it may be found that, when prepared in slightly different ways, the properties of the solids show fairly large differences in magnetic behaviour. The high susceptibility indicated for Na_2An is of the same order as for some of the metallic rare earths. Further studies are being made as stated below. Electrical properties of different samples were quite reproducible, but insufficient magnetic measurements could be achieved to test whether this was also true for the magnetic properties. The free radical would appear to have one uncoupled spin, and would thus exhibit increasing paramagnetism with falling temperature (Selwood, " Magnetochemistry," Interscience Publ., New York, 1943).

When the ratio of sodium to anthracene rises, the paramagnetism is greatly increased, but the temperature coefficient sinks to a much lower value. Eventually the paramagnetism becomes comparable with the values observed per g.-atom of sodium in sodium–ammonia solutions (see below).

Electrical Conductance.—The solids show marked positive temperature coefficients. For complexes with approximately the same composition activation energies are in the same sequence as the ionisation energies of the metals (Table 4).

Apart from variation in the alkali metal, the effect of varying the composition with a

given alkali metal has noteworthy effects on the conductance parameters, as might be expected if the solid behaves as a semi-conductor with an adjustable number of electron-donor atoms and electron-acceptor molecules in the crystal.

TABLE 4.

Compound	E (ev)	Ionisation potential, I	E/I
$Li_{1\cdot16}An$	1·34	5·39	0·25
$Na_{1\cdot08}An$	1·20	5·14	0·23
$K_{1\cdot18}An$	1·10	4·34	0·25

As the anthracene is progressively extracted by elutriation from the solid, the electrical conductance rises steeply, and the activation energy E sinks (Table 2). This might perhaps be attributed to the removal by the solvent of diluent crystals of anthracene, or of mono-sodium anthracene, from a more highly conducting disodium anthracene. However, the accompanying changes in magnetic properties (Table 1) indicate that solvent-extraction of some of the hydrocarbon involves a much more fundamental change for the mobile π-electrons than would be realised merely on removing one component from a mechanical mixture of different crystals. Further discussion is deferred pending the investigation of more highly compressed powders and of complexes with other aromatic molecules.

When a solvent-free solid is compared with a solid retaining some ether (Figs. 4 and 5), notwithstanding striking differences in colour, the properties are similar. Too much weight cannot be put on this conclusion, since analysis suggests that part of the ether was lost during handling. Fig. 5*A* may indeed refer to mechanical mixtures of ether-retaining and solvent-free complexes.

Analogy between the Alkali Metal–Hydrocarbon Solids and Alkali Metal–Liquid Ammonia Solutions.—As has been described above, the changes in properties observed on removal of anthracene, by extraction with solvents or by vaporisation, suggest that the complexes behave as solid solutions with semiconducting properties.

Considerable attention has been devoted to the remarkable physical and chemical properties of solutions of alkali metals in liquid ammonia (Hüster, *Ann. Physik*, 1938, **33**, 498; Farkas, *Z. physikal. Chem.*, 1932, **161**, 355; Krauss and Lucasse, *J. Amer. Chem. Soc.*, 1922, **44**, 1941, 1949). It is suggested that the alkali metal–hydrocarbon solids now isolated have analogous properties in certain respects. Compared with this particular hydrocarbon, at corresponding bulk concentrations the specific conductance is much higher with ammonia as solvent for the sodium. But although the conductances differ widely for the two systems, in the solid complexes now studied allowance must be made for considerable intergranular resistance (cf. McDonnell, Pink, and Ubbelohde, *loc. cit.*). The conductance of sodium anthracene shows a steep rise with increase in mole-fraction of sodium, not unlike the rise for $Na–NH_3$. This suggests that the electrons from the sodium atoms acquire a limited freedom of mobility in the solid owing to the (moderate) electron affinity of the anthracene. The solid solution may be thought to consist of a giant assemblage of neutral and ionised sodium atoms, and neutral and negative anthracene molecules. Some bond formation may also occur between neighbouring anthracene molecules in 10 : 10′-positions. Finite, but not very large activation energy appears to be required for the electrons to migrate from one anthracene molecule to the next. Bowen (*J. Chem. Phys.*, 1945, **13**, 306; *Quart. Reviews*, 1947, **1**, 1) has shown that migration of " excitons " is quite extensive in the anthracene lattice.

In making magnetic comparisons with $Na–NH_3$, intercrystalline barriers in the powders should have much less influence. On the convention that the susceptibility of

TABLE 5. *Apparent atomic susceptibility of sodium in sodium anthracene.*

Compound	$Na_{1\cdot42}An$	$Na_{1\cdot70}An$	$Na_{1\cdot96}An$	$Na_{2\cdot02}An$
$10^6\,\chi_{Na}$	+117·0	+85·7	+103·7	+424·0

the electron-accepting molecule (ammonia or anthracene) remains constant, this is subtracted from the combined value for the complex to obtain the apparent susceptibility of the dissolved sodium atoms, in Table 5.

Though the numerical results must be regarded with caution, it seems noteworthy that

in the Na–NH_3 systems the susceptibility of sodium reaches quite similar values of paramagnetism, but at higher dilutions.

So far as it goes, the present evidence is against the possibility that electron transfer in the complexes proceeds as far as complete ionisation. The shift of the ultra-violet absorption bands of the anthracene into the visible region, owing to partial transfer of the electrons to anthracene in the solvated and solvent-free complexes, may be compared with effects in the spectra of other substituted aromatic hydrocarbons. The inclusion in the nucleus of electron-donating groups such as NH_2 or CH_3 is well known to cause a shift toward longer wave-lengths. Sodium anthracene is probably more like sodium antimonide than sodium nitride in the electronic character of the solid. Analogies can also be suggested with some of the metallic sulphides, selenides, and tellurides.

Thanks are offered to Dr. R. C. Pink for valuable help in studying the magnetic and other properties, and to Miss I. Woodward for discussions about the *X*-ray findings, also to Imperial Chemical Industries Limited for the loan of apparatus for magnetic measurements.

QUEEN'S UNIVERSITY, BELFAST. [*Received, September 7th,* 1953.]

Studies in the Steroid Group. Part LXIV. Some Reactions starting from 3β-Acetoxy-9α : 11α-epoxyergosta-7 : 22-diene.*

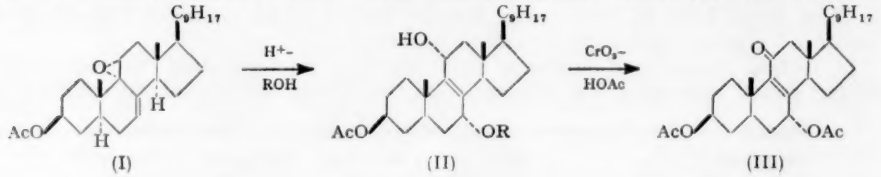
By H. B. HENBEST and A. A. WAGLAND.

[Reprint Order No. 4704.]

The above Δ^7-9 : 11-epoxide (I), when treated successively with the boron trifluoride–ether complex, monoperphthalic acid, and alkali, yields the 7β-hydroxy-$\Delta^{8(9)}$-11-ketone (VIII). The 7 : 11α-diol produced on acid-catalysed hydration of the 9 : 11-epoxide (I) is shown to contain a 7α-hydroxyl group, for acetolysis of the epoxide followed by oxidation affords the isomeric 7α-hydroxy-$\Delta^{8(9)}$-11-ketone (III).

RECENT work has shown that treatment of the 9α : 11α-epoxide (I) with dilute mineral acids yields a 7 : 11-dihydroxy-$\Delta^{8(9)}$-steroid as the primary product (Heusser, Eichenberger, Kurath, Dällenbach, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 2106; Budziarek, Johnson, and Spring, *J.*, 1952, 3410). The 11-hydroxyl group in this compound has been assigned an α-configuration in view of the ready formation of a 3 : 7 : 11-triacetate, but the stereochemistry of the entering 7-hydroxyl group has not been established.

In order to gain further information about this 7 : 11-diol and its mode of formation, the reaction between (I) and acetic acid was studied. The formation of the 7 : 11-diol can be envisaged as (nucleophilic) solvent attack at $C_{(7)}$ on the conjugate acid of (I)—accordingly, substitution of acetic acid for water should give a 7-acetoxy-11-hydroxy-compound (*e.g.*, II; R = Ac). Suitable conditions for the acetolysis of (I) were found with acetic acid–dioxan solutions at 50°, the rotation changing smoothly from the initially negative value to a finally constant positive value. Analysis of the reaction product, isolated in



(I) (II) (III)

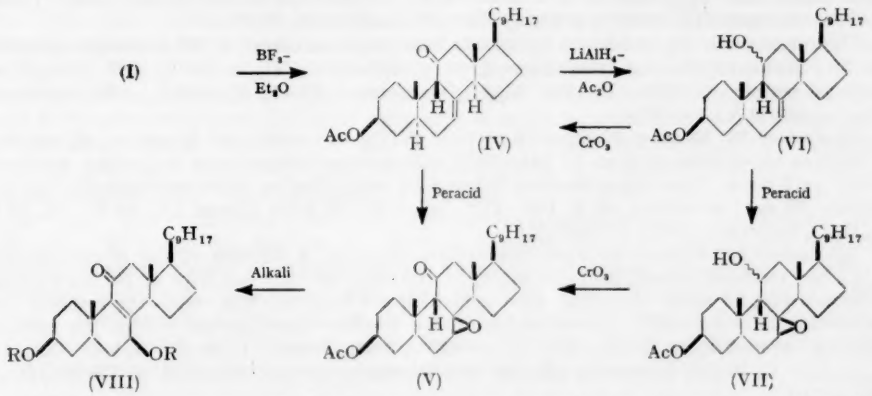
50—60% yield, indicated addition of acetic acid to (I), and the structure (II; R = Ac; 7α-configuration for reasons discussed later) was further indicated by the very ready oxidation (chromic acid in acetic acid rapidly oxidises allylic secondary alcohols; cf.

* Part LXIII, *J.*, 1954, 125.

Henbest and Jones, *J.*, 1948, 1792) to a conjugated ketone (III) (unreactive carbonyl group), and by acetylation to the triacetate obtained previously by acetylation of the known 7 : 11-diol.

The formation of the 7-acetate (II; R = Ac) confirms the mechanism discussed above, but the configuration of the 7-acetate group remained to be decided. This was shown to be α-orientated * by preparing the isomeric 7β-acetoxy-$\Delta^{(8)9}$-11-ketone (VIII; R = Ac) by another route. The boron trifluoride–ether complex isomerises (I) to an 11-oxo-Δ^{7}-9β-steroid (IV) (Heusler and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 398; Part LXII of this series, *J.*, 1953, 2921). The Δ^{7}-bond in (IV), in marked contrast to those in 9α-compounds, is readily hydrogenated, to yield a saturated 11-ketone (cf. Part LXII). This hydrogenation is stereospecific, proceeding by frontal attack of catalyst to yield an 8β : 9β-steroid exclusively.

The Δ^{7}-bond in (IV) reacts preferentially with monoperphthalic acid, to yield the epoxide (V) (Heusler and Wettstein, *loc. cit.*, also prepared this oxide but did not consider its configuration). A β-configuration is assigned to the 7 : 8-epoxy-group in view of the similar stereochemical courses taken by hydrogenation and peracid reactions with other trisubstituted olefinic bonds in the steroid series. It was just possible that epimerisation at $C_{(9)}$ had occurred during the peracid reaction with (IV), for Δ^{7}-9β-11-ketones isomerise very easily to 9α-compounds (Part LXII). However, the 9β-structure for (V) was confirmed by its preparation by an alternative route. Lithium aluminium hydride reduction (and reacetylation) converted (IV) into (VI), which still retained the β-$C_{(9)}$-configuration, for oxidation yielded the original ketone (IV) [the $C_{(11)}$-stereochemistry of (VI) will be discussed in a later paper]. Peracid oxidation of (VI) afforded the 7β : 8β-epoxide (VII) [hydrogenation of (VI) also proceeds by frontal attack, unpublished work], which on oxidation gave the 7β : 8β-epoxy-9β-11-ketone (V), identical with that prepared previously.



Alkaline rearrangement of (V) was followed spectroscopically, the maximum intensity (ε) reached under the conditions chosen being 5800 (the isolated pure diol had ε = 9000). Plotting the concentration of unsaturated ketone against time gave a smooth curve, which indicated that no appreciable amount of the 9α-epimer of (V) was being formed as an intermediate : alkali-assisted removal of the 9β-proton is therefore probably accompanied directly by movement of the negative charge on to the $C_{(7)}$-oxygen. Acetylation of the reaction product yielded (VIII; R = Ac), different from the conjugated ketone (III)

* Two possible reasons may be suggested for the acetate group's entering in the α-configuration at $C_{(7)}$. First, the reaction may simply be another example of "rear attack" which often takes place with steroids of natural configuration, but, secondly, the fact that the original epoxide group and the entering group have the same configuration may be significant, *i.e.*, for electrostatic reasons the acetate (anion) may approach from the same side as the (protonated) epoxide group. Both factors may operate in this instance. The possible importance of the second factor is supported by earlier suggestions of Winstein and Young for which Stork and White (*J. Amer. Chem. Soc.*, 1953, **75**, 4119) have recently provided further experimental support.

obtained previously *via* the acetolysis reaction, which must therefore contain a 7α-acetoxyl group.

It has been noted previously (Henbest, Jones, Wood, and Woods, *J.*, 1952, 4894) that γ-oxygenated αβ-unsaturated ketones often absorb at shorter wave-lengths in the ultra-violet than the corresponding unsubstituted compounds. The 7α- and the 7β-acetate (III and VIII; R = Ac) provide further examples of this effect, $\lambda_{max.}$ being at 2490 Å in each case, compared with 2540 Å observed with 3β-acetoxyergosta-8 : 22-dien-11-one.

Experimental

General experimental directions are as given in Part LXI, *J.*, 1953, 2916.

3β : 7α-*Diacetoxyergosta*-8 : 22-*dien*-11α-*ol* (II; R = Ac).—A solution of 3β-acetoxy-9α : 11α-epoxyergosta-7 : 22-diene (1 g.) in dioxan (40 c.c.) and acetic acid (40 c.c.) was kept at 50° for 2 days. The product was isolated with ether and chromatographed on deactivated alumina (100 g.). Light petroleum–benzene (3 : 1) eluted starting material (25 mg.), but light petroleum–benzene (1 : 3) yielded material which crystallised from aqueous acetone as needles (600 mg.), m. p. 140—147°. Further crystallisation gave the pure *compound*, m. p. 158—162°, $[\alpha]_D$ +83° (*c*, 2·1) (Found: C, 74·7; H, 9·8. $C_{32}H_{50}O_5$ requires C, 74·75; H, 9·8%). Acetylation gave the 3β : 7α : 11α-triacetate, m. p. 169—171° (undepressed on admixture with an authentic sample), $[\alpha]_D$ +93° (*c*, 1·1).

3β : 7α-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (III).—Solutions of the above 11-alcohol (2 g.) in acetone (20 c.c.) and chromic acid (290 mg.) in acetic acid (58 c.c.) were mixed and kept at 20° for 2 hr. The green solution was concentrated to a small bulk under reduced pressure and the steroid isolated with ether. The product in benzene was filtered through deactivated alumina (50 g.), to give material (1·8 g.) which when crystallised from methanol afforded *ketone*, m. p. 102—105°, $[\alpha]_D$ +109° (*c*, 0·8) (Found: C, 74·8; H, 9·4. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). In the first preparations of this compound a (subsequently unstable) modification was obtained, m. p. 68—70°; the rotation and light absorption of the two forms were identical. Light absorption: $\lambda_{max.}$ 2490 Å; ε = 8500. Infra-red spectrum (on supercooled melt): peaks at 1735, 1250 (acetate), 1670 (11-ketone), 1595 (Δ^8), and 980 cm.$^{-1}$ (Δ^{22}).

Hydrolysis with 5% potassium hydroxide solution in methanol at 20° overnight afforded the 3β : 7β-*diol* (crystallised from acetone), m. p. 202—205°, $[\alpha]_D$ +149° (*c*, 0·5) (Found, in sublimed sample: C, 78·55; H, 10·5. $C_{28}H_{44}O_3$ requires C, 78·45; H, 10·35%). Light absorption, $\lambda_{max.}$ 2510 Å; ε = 9400.

3β-*Acetoxy*-7β : 8β-*epoxy*-9β-*ergost*-22-*en*-11-*ol* (VII).—A solution of 3β-acetoxy-9β-ergosta-7 : 22-dien-11ξ-ol (200 mg.; m. p. 165—168°) and monoperphthalic acid (1·1 mols.) was kept at 20° for 7 days. Isolation with ether followed by crystallisation from methanol afforded the *epoxide* (90 mg.) as needles, m. p. 190—210°, $[\alpha]_D$ +61° (*c*, 0·83) (Found: C, 76·25; H, 10·3. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·25%).

3β-*Acetoxy*-7β : 8β-*epoxy*-9β-*ergost*-22-*en*-11-*one* (V).—(*a*) A solution of the Δ^7-steroid (IV) (1 g.) and monoperphthalic acid (1·1 mols.) in dry ether (40 c.c.) was kept at 20° for 3 weeks (alternatively, 10 mols. of peracid were used with a 7 hour reaction time—the reaction was followed polarimetrically). Crystallisation of the product from acetone yielded the epoxide (750 mg.) as needles, m. p. 175—177°, $[\alpha]_D$ −63° (*c*, 0·82) (Found: C, 76·45; H, 9·8. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%) (Heusler and Wettstein, *loc. cit.*, record m. p. 170·5—171·5°, $[\alpha]_D$ −74°).

(*b*) Solutions of (VII) (450 mg.) in acetone (25 c.c.) and chromic acid (8N; cf. *J.*, 1951, 2402) were mixed and kept at 20° for 5 min. Isolation with ether and crystallisation gave a good yield of the epoxy-ketone, m. p. 173—175°, $[\alpha]_D$ −63° (*c*, 0·46). Infra-red spectrum (in CS_2): peaks at 1730, 1250 (acetate), 1715 (shoulder, 11-ketone), and 970 cm.$^{-1}$ (Δ^{22}).

3β : 7β-*Diacetoxyergosta*-8 : 22-*dien*-11-*one* (VIII; R = Ac).—A solution of the foregoing 7β : 8β-epoxide (2 g.) and potassium hydroxide (4 g.) in methanol (400 c.c.) was kept at 20°. The concentration of conjugated ketone (estimated spectroscopically) reached a maximum after 5½ hr., thereafter slowly declining. The product was isolated (after 5½ hr.) with ether, acetylated in the usual way overnight, and then crystallised from methanol, to yield the 3β : 7β-*diacetate* (1·3 g.), m. p. 149—152°, $[\alpha]_D$ +83° (*c*, 0·95) (Found: C, 75·15; H, 9·65. $C_{32}H_{48}O_5$ requires C, 74·95; H, 9·45%). Light absorption: λ_{max} 2490 Å; ε = 8700. Infra-red spectrum (in Nujol): peaks at 1730, 1240 (acetate), 1658 (11-ketone), and 1593 cm.$^{-1}$ (Δ^8). In another experiment, the reacetylation stage was omitted and the 3β : 7β-*diol* (VIII; R = H) was isolated; it crystallised from acetone as needles, m. p. 213—217°, $[\alpha]_D$ +149° (Found: C, 75·4;

H, 10·35. $C_{28}H_{44}O_3,H_2O$ requires C, 75·3; H, 10·4%). Light absorption: $\lambda_{max.}$ 2530 Å; $\varepsilon = 9000$.

We are indebted to Professor E. R. H. Jones, F.R.S., for encouragement and interest in this work, Glaxo Laboratories Ltd., for gifts of materials, and the Department of Scientific and Industrial Research for a maintenance grant (to A. A. W.). Microanalyses were performed by Mr. E. S. Morton and Mr. H. Swift, and infra-red spectra were determined under the direction of Dr. G. D. Meakins.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 7th*, 1953.]

Studies in the Steroid Group. Part LXV. Reactions of 11-Hydroxy- and 11-Oxo-5α-steroids.*

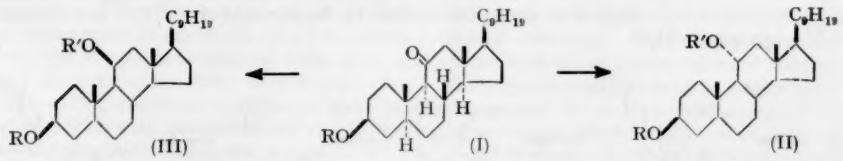
By A. CRAWSHAW, H. B. HENBEST, and E. R. H. JONES.

[Reprint Order No. 4705.]

Reduction of 11-oxo-steroids gives 11α- or 11β-hydroxy-compounds. It is shown that the more hindered 11β-hydroxy-steroids can be acetylated with acetyl chloride. Phosphorus oxychloride–pyridine dehydration of epimeric 11-hydroxy-compounds affords the same $\Delta^{9(11)}$-olefin. As in the 5β-series, enol acetylation of 11-oxo-5α-steroids yields 11-acetoxy-$\Delta^{9(11)}$-steroids. The formation of $\Delta^{9(11)}$-compounds in these reactions indicates the relative difficulty of forming the strained Δ^{11}-system.

THE starting material for most of the work described in this paper was 3β-acetoxyergostan-11-one (I), a compound first described by Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2106). 11α-Hydroxy(equatorial)-compounds have been prepared recently by sodium–propanol reduction of 11-ketones (Heusser, Anliker, and Jeger, *ibid.*, 1952, **35**, 1537; Herzog, Jevnik, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 269). This reduction has also been effected independently with sodium–ethanol, and although some starting material remains it is easily removed during chromatographic purification. The 3β : 11α-diol (II; R = R′ = H) was readily converted into its diacetate.

It is now well established that lithium aluminium hydride reduction of 11-ketones yields predominantly 11β-hydroxy(polar)-steroids, *e.g.*, (I) gives (III; R = R′ = H) in high yield. 11β-Hydroxy-groups have not been acylated hitherto.† 11β-Acetates (*e.g.*, III; R = R′ = Ac) can however be obtained in good yield by acetylation with acetyl chloride–dimethylaniline in chloroform (cf. formation of tertiary 5α-acetates; Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513; Part LVI of this series, *J.*, 1952, 4883). 11β-Hydroxy-Δ^7-steroids are also acetylated by this method (to be published) (cf. Oliveto, Gerold, and Hershberg, *Arch. Biochem. Biophys.*, 1953, **43**, 234, who have also described acetylation of 11β-hydroxy-compounds by different methods).

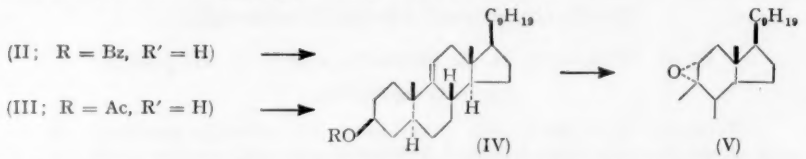


The behaviour of 11α- and 11β-hydroxy-compounds with phosphorus oxychloride in pyridine was then studied. This reagent usually affords trisubstituted olefins when the groups to be eliminated are *trans* and polar (cholestan-4β-ol ⟶ cholest-4-ene, Barton

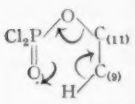
* Part LXIV, *J.*, 1954, preceding paper.

† Cf. Fieser and Fieser ("Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, p. 408), but Reichstein and Steiger (*Helv. Chim. Acta*, 1937, **20**, 819) probably obtained an 11β-acetate by vigorous treatment with acetic anhydride and pyridine.

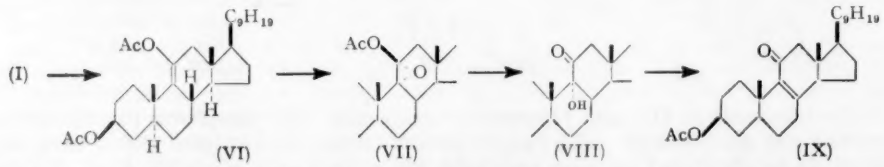
and Rosenfelder, *J.*, 1951, 1048; formation of Δ^7-compounds from 7α-hydroxy-steroids, Buser, *Helv. Chim. Acta*, 1947, **30**, 1379; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226; Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284—the last paper records that some 7β-chloro-compound may also be formed). Treatment of the 11β-hydroxy-compound (III; R = Ac, R′ = H) with phosphorus oxychloride in pyridine gave the expected olefin (IV; R = Ac) in 70% yield; the $\Delta^{9(11)}$-rather than the Δ^{11}-structure is assigned from the infra-red absorption characteristics (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Henbest, Meakins, and Wood, *J.*, 1954, in the press). The homogeneity of this dehydration product was confirmed by its conversion (in high yield) into a single (9α : 11α-)epoxide (see Experimental section); the rotation contribution of the $\Delta^{9(11)}$-bond is also discussed in the Experimental section. Hydrogenation of the olefin in acetic acid (platinum catalyst) gave ergostanyl acetate.



The reaction of 11α-hydroxy-steroids with phosphorus oxychloride was less easy to predict. In analogous examples, cholestan-4α-ol gave a phosphate, and 7β-hydroxy-compounds yielded 7α-chloro-steroids (cf. refs. given above for 4β- and 7α-hydroxy-derivatives). The 3β : 11α-diol (II; R = R′ = H) was converted into its 3β-monobenzoate by selective acylation with benzoic anhydride in pyridine (Eckhardt, *Ber.*, 1938, **71**, 461). This, with phosphorus oxychloride–pyridine, also gave a $\Delta^{9(11)}$-compound (IV; R = Bz) (40% yield) as the only isolable product, hydrolysis yielding ergost-9(11)-en-3β-ol, identical with that obtained from the above 3β-acetate. The formation of a $\Delta^{9(11)}$-compound is unusual under these conditions, representing a *cis*-elimination of groups. The reaction may be an E_1 process occurring by loss of proton from $C_{(9)}$ from a positively charged $C_{(11)}$-intermediate, or a cyclic intermediate may possibly be involved (see inset). The further possibility (suggested by a referee) that a normal *E*2 reaction might follow the intermediate formation of an 11β-chloro-compound seems unlikely since Heusler and Wettstein (*loc. cit.*) record that 7α-chloro-steroids, of analogous stereochemistry, are stable in boiling collidine.



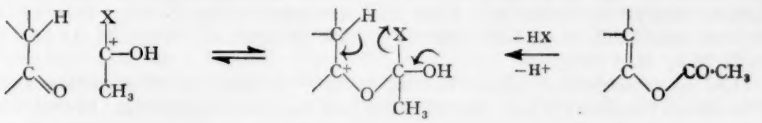
The direction of enol acetylation of 11-oxo-5α-steroids has also been investigated. Previous work on this type of reaction has been concerned with 5β-compounds, where recent studies (Hirschmann and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 2361) have shown that 11-acetoxy-$\Delta^{9(11)}$-5β-steroids are formed. The conversion of the 11-ketone (I) into its enol acetate was effected with acetic anhydride (Marshall, Kritchevsky, Lieberman, and Gallagher, *ibid.*, 1948, **70**, 1837) or with *iso*propenyl acetate (Moffet and Weisblat, *ibid.*, 1952, **74**, 2183). The enol acetate was separated from some unchanged 11-ketone by chromatography, and was then converted in high yield into the corresponding 9α : 11α-epoxide (VII).



Alkaline hydrolysis of (VII) afforded the ketol (VIII), in which the hydroxyl group was not acetylated under mild conditions. Thionyl chloride–pyridine dehydration of (VIII) yielded the Δ^8-11-ketone (IX) (cf. Part LXII, *J.*, 1953, 2921), proving that the original enol acetate contained a $\Delta^{9(11)}$-linkage (VI). The 9β-11-ketone (Part LXII),

isomeric with (I), was recovered largely unchanged when subjected to conditions which gave 50% of enol acetate from (I); the non-epimerisation at $C_{(9)}$ under these acidic conditions is noteworthy (cf. Part LXII).

The results of enol acetylation experiments in the steroid series may be rationalised in terms of a transition complex (see formulæ), in which X may be OAc, O·CMe:CH_2, or halogen. The transformation of the intermediate complex into an enol acetate will be dependent upon steric factors; in particular, the accessibility of the hydrogen atom to be removed will be of great importance, as suggested by Cornforth (*Ann. Reports*, 1952, **49**, 197). The formation of $\Delta^{20(21)}$-20-acetates (in preference to the more stable $\Delta^{17(20)}$-20-acetates) in the lower-temperature (*iso*propenyl acetate) method of acetylating 20-ketones, and the more readily acetylation of 9α-11-ketones compared with the 9β-compounds (9β- less accessible than 9α-hydrogen) are reactions, both of which indicate the importance of the steric accessibility of a hydrogen atom adjacent to the ketone group. The higher reaction temperature employed in the acetic anhydride procedure may cause the ultimate



production of the thermodynamically more stable product (cf. conversion of $\Delta^{20(21)}$- into $\Delta^{17(20)}$-20-acetates). In this connection it may be noted that the direction of enol acetylation of a 7-oxo-5β-steroid (to give a Δ^{6}-compound; Hirschmann and Wendler, *loc. cit.*) is analogous to the formation of a Δ^{3}-3-acetate from a 3-oxo-5β-steroid (Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1952, **74**, 3852). A 7-oxo-5α-steroid should yield a Δ^{7}-compound since 3-oxo-5α-steroids give Δ^{2}-3-acetates (*loc. cit.*).

Infra-red absorption measurements indicate that the double bond in Δ^{11}-steroids is appreciably strained (Henbest, Meakins, and Wood, *loc. cit.*), and there appears to be a growing amount of chemical evidence that the formation of a Δ^{11}-compound will not take place if an alternative reaction path is available. The reactions described in this paper which have led to $\Delta^{9(11)}$-steroids indicate that the alternative formation of a Δ^{11}-compound in each case is prevented by unfavourable energy relations. Difficulty in forming Δ^{11}-steroids is also indicated by the rather poor yields (*ca.* 25%) of Δ^{11}-compounds from base-assisted elimination of polar 12α-tosyloxy-groups (Meystre and Wettstein, *Helv. Chim. Acta*, 1948, **31**, 1890; von Euw and Reichstein, *ibid.*, p. 2076), and the ring-contraction reaction of 12β-toluene-*p*-sulphonates (Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1952, **74**, 2693) which occurs (solvolysis conditions) in preference to E_1 elimination to give a Δ^{11}-compound.

Experimental

General experimental directions are as given in Part LXI, *J.*, 1953, 2916; infra-red spectra were determined as mulls in Nujol unless stated otherwise.

Preparation of 11α-*Hydroxy-compounds.*—Sodium (25 g.) was added during 1 hr. to a solution of 3β-acetoxyergost-22-en-11-one (2 g.) in absolute ethanol (500 c.c.). When the sodium had dissolved, the steroid was isolated with ether and chromatographed on deactivated alumina (100 g.). Benzene–ether (20 : 1) (800 c.c.) eluted 3β-hydroxyergost-22-en-11-one (500 mg.), m. p. 171—173°, which on acetylation gave starting material, m. p. 125—126°, $[\alpha]_D$ +12°. Continued elution with benzene–ether (1 : 1) (600 c.c.) gave ergost-22-ene-3β : 11α-diol (1·01 g.) (crystals from nitromethane), m. p. 165—167°, $[\alpha]_D$ −21° (Found: C, 80·5; H, 11·5. Calc. for $C_{28}H_{48}O_2$: C, 80·7; H, 11·6%). Heusser *et al.* (*Helv. Chim. Acta*, 1952, **35**, 950) record m. p. 156—157°, $[\alpha]_D$ −16°. Acetylation of the 3β : 11α-diol gave the diacetate, crystallising from methanol as needles, m. p. 137—138°, $[\alpha]_D$ −35° (Found: C, 76·65; H, 10·5. Calc. for $C_{32}H_{52}O_4$: C, 76·75; H, 10·45%). Heusser *et al.* (*loc. cit.*) give m. p. 126—127°, $[\alpha]_D$ −36°.

A solution of the 3β : 11α-diol (750 mg.) in dioxan (40 c.c.) and acetic acid (40 c.c.) was shaken with hydrogen in the presence of Adams catalyst (300 mg.). Crystallisation from nitromethane afforded *ergostane*-3β : 11α-*diol* (II; R = R′ = H) (650 mg.), m. p. 158·5—160°, $[\alpha]_D$ −2° (Found: C, 80·35; H, 12·1. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·05%). Acetic anhydride and

pyridine (overnight at 20°) gave the *diacetate* (II; R = R′ = Ac), m. p. 89—91°, $[\alpha]_D$ −21° (Found : C, 76·15; H, 10·95. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85%).

A solution of ergostane-3β : 11α-diol (1·3 g.) and benzoic anhydride (1·3 g.) in pyridine (60 c.c.) was heated under reflux for 24 hr. The steroid was isolated with ether and chromatographed on alumina (140 g.). Benzene–ether (9 : 1) (1·5 l.) eluted solid (830 mg.) which on crystallisation from methanol gave 3β-*benzoyloxyergostan*-11α-ol (II; R = Bz, R′ = H) (640 mg.), m. p. 176—178°, $[\alpha]_D$ −5° (Found : C, 80·1; H, 10·55. $C_{35}H_{54}O_3$ requires C, 80·4; H, 10·4%). Infra-red spectrum (in CCl_4) : peaks at 3630 (OH), 1715 and 1275 cm.$^{-1}$ (benzoate). Further elution of the column with ether yielded starting material (550 mg.).

Preparation of 11β-*Hydroxy-compounds.*—3β-Acetoxyergost-22-en-11-one (1·5 g.) in dry ether (30 c.c.) was treated with lithium aluminium hydride (2 mols.) in ether (20 c.c.), the mixture then being heated under reflux for 1 hr. Ethyl acetate (5 c.c.) was added, followed by aqueous tartaric acid. Isolation with ether and acetylation of the product with acetic anhydride and pyridine at 20° overnight gave material (1·37 g.), which yielded 3β-*acetoxyergost*-22-*en*-11β-*ol* (1·2 g.) (as needles from methanol), m. p. 170—171°, $[\alpha]_D$ −6° (Found : C, 78·55; H, 10·8. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). Hydrogenation of this compound with Adams catalyst in acetic acid gave 3β-*acetoxyergostan*-11β-*ol* (III; R = Ac, R′ = H) (needles from methanol), m. p. 134—135°, $[\alpha]_D$ +25° (Found : C, 78·05; H, 11·45. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

3β : 11β-*Diacetoxyergostane* (III; R = R′ = Ac).—A solution of ergostane-3β : 11β-diol (0·5 g.) in dimethylaniline (12 c.c.), acetyl chloride (6 c.c.), and chloroform (18 c.c.) was heated under reflux for 16 hr. The steroid was isolated with ether, and then percolated in benzene solution through alumina (30 g.). Crystallisation from methanol gave the *diacetate* (250 mg.), m. p. 118—119°, $[\alpha]_D$ +31° (Found: C, 76·6; H, 11·15. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85%). Infra-red spectrum (in CCl_4) : peaks at 1735 and 1235 cm.$^{-1}$ (acetate); no hydroxyl band.

Dehydration of 11-*Hydroxy-compounds.*—(*a*) Phosphorus oxychloride (4 c.c.) was added to a solution of 3β-benzoyloxyergostan-11α-ol (640 mg.) in pyridine (14 c.c.) with external cooling. The solution was kept at 20° overnight and the steroid was isolated with ether. The solid product (560 mg.) was chromatographed on alumina (55 g.); light petroleum–benzene (9 : 1) (500 c.c.) eluted material which, on crystallisation from methanol–chloroform, afforded 3β-*benzoyloxyergost*-9-*ene* (250 mg.), m. p. 153·5—154·5°, $[\alpha]_D$ +16° (Found : C, 83·1; H, 10·65. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). Infra-red spectrum : peaks at 1715, 1285 (benzoate), 845 and 820 cm.$^{-1}$ (Δ^9-H bending). Hydrolysis gave *ergost*-9-*en*-3β-*ol* (IV; R = H) (crystals from methanol), m. p. 147·5—149°, $[\alpha]_D$ +29° (Found : C, 83·7; H, 12·1. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). Acetylation yielded 3β-*acetoxyergost*-9-*ene* (needles from methanol), m. p. 128—132°, $[\alpha]_D$ +17° (Found : C, 81·3; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Infra-red spectrum (supercooled melt) : peaks at 1730, 1235 (acetate), 3045 (sh), 1640, 840, and 820 cm.$^{-1}$ (Δ^9).

(*b*) Phosphorus oxychloride (0·75 c.c.) was added to 3β-acetoxyergostan-11β-ol (150 mg.) in pyridine (4 c.c.), and the solution kept at 20° for 12 hr. Isolation of the steroid as usual followed by crystallisation from methanol afforded 3β-acetoxyergost-9-ene, with physical properties (including infra-red spectrum) identical with those of the specimen prepared by method (*a*). Hydrolysis yielded the same 3β-hydroxy-compound.

Since these compounds are the simplest $\Delta^{9(11)}$-5α-steroids yet prepared it was of interest to calculate the rotation contribution of the $\Delta^{9(11)}$-bond. With the 3β-hydroxy-compounds, ΔE = + 44, and with the 3β-acetates, ΔE = + 58°. These figures are similar to those given by Barton and Klyne (*Chem. and Ind.*, 1948, 755), for 5β-compounds. Fieser and Huang (*J. Amer. Chem. Soc.*, **1953, 75,** 5356) have reported ΔE values of +15° and +36° for cholest-9-en-3β-ol and its acetate respectively.

Hydrogenation of *Ergost*-9-*en*-3β-*ol.*—A solution of the sterol (30 mg.) in acetic acid (3 c.c.) was shaken with Adams catalyst (30 mg.) and hydrogen for 1 hr. Crystallisation of the product from methanol gave ergostan-3β-ol, m. p. and mixed m. p. 143—146°, $[\alpha]_D$ +18°. Hydrogenation in ethyl acetate solution for 90 min. afforded partly reduced material, m. p. 149—150°, $[\alpha]_D$ +23°.

3β-*Acetoxy*-9α : 11α-*epoxyergostane* (V).—Solutions of 3β-acetoxyergost-9-ene (1·2 g.) in ether (15 c.c.) and monoperphthalic acid (0·6N in ether) (2 mols.) were mixed and then kept at 20° for 5 days. The 9α : 11α-*epoxide* (0·85 g.), isolated as usual, crystallised from methanol–chloroform as needles, m. p. 167—168°, $[\alpha]_D$ −12° (Found : C, 78·8; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). Chromatography of part (125 mg.) of the mother-liquor material yielded a further amount (100 mg.) of the pure epoxide.

Enol Acetylation of 11-*Oxo-steroids.*—(a) *With acetic anhydride.* A mixture of 3β-acetoxyergostan-11-one (0·9 g.), toluene-*p*-sulphonic acid (0·38 g.), and acetic anhydride (70 c.c.) was distilled slowly for 5 hr., the solution becoming pale-brown and decreasing in volume to about 10 c.c. The steroid product (0·94 g.) was chromatographed on deactivated alumina (95 g.). Development with light petroleum–benzene (9 : 1) (1 l.) gave starting material (260 mg.), m. p. 139—140°, and further elution with the same solvent yielded an oil (500 mg.), which crystallised slowly from methanol, to give 3β : 11-*diacetoxyergost*-9-*ene* (VI) (350 mg.) as prisms, m. p. 78—80·5°, $[\alpha]_D$ +39° (Found: C, 76·8; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). Infra-red spectrum (in CCl_4) : peaks at 1745, 1220 (11-acetate), 1735, 1235 (3-acetate), and 1650 cm.$^{-1}$ (Δ^9). Similar treatment of 3β-acetoxy-9β-ergostan-11-one for 6 and for 20 hr. periods gave 80% and 70% yields respectively of starting material, no enol acetate being isolated.

(b) *With* iso*propenyl acetate.* A mixture of 3β-acetoxyergostan-11-one (250 mg.), toluene-*p*-sulphonic acid (50 mg.), and *iso*propenyl acetate (10 c.c.) was distilled slowly for 10 hr. As the volume of solution reached about 5 c.c., fresh portions (5 c.c.) of *iso*propenyl acetate were added (3 times). Chromatography of the product afforded starting material (160 mg.), m. p. 138—140°, and 3β : 11-diacetoxyergost-9-ene (50 mg.), m. p. and mixed m. p. 75—79°.

3β : 11β-*Diacetoxy*-9α : 11α-*epoxyergostane* (VII).—An ethereal solution of monoperphthalic acid (2 mols.) was added to 3β : 11-diacetoxyergost-9-ene (300 mg.) in dry ether (4 c.c.), and the mixture was kept at 0° for 1 day and then at 20° for 6 days. Isolation with ether followed by crystallisation from methanol afforded the *epoxide* (250 mg.) as fine needles, m. p. 162·5—163·5°, $[\alpha]_D$ +32° (Found: C, 74·0; H, 10·15. $C_{32}H_{52}O_5$ requires C, 74·35; H, 10·15%). Infra-red spectrum : peaks at 1740, 1235 (11-acetate), 1730 and 1245 cm.$^{-1}$ (3-acetate).

3β-*Acetoxy*-9α-*hydroxyergostan*-11-*one* (VIII).—Methanolic potassium hydroxide (8 c.c.; 5%) was added to the foregoing epoxide (200 mg.) dissolved in methanol (10 c.c.), the mixture being heated under reflux for ¾ hr. Isolation with ether and crystallisation from nitromethane gave a high yield of 3β : 9α-*dihydroxyergostan*-11-*one*, m. p. 189—190°, $[\alpha]_D$ +59° (Found: C, 77·6; H, 11·15. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Infra-red spectrum : peaks at 3150, 3580 (OH), and 1695 cm.$^{-1}$ (11-ketone). Acetylation with acetic anhydride–pyridine at 20° overnight afforded the 3β-*acetate* (crystals from nitromethane–methanol), m. p. 181—182°, $[\alpha]_D$ +48° (Found: C, 75·7; H, 10·7. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Infra-red spectrum : peaks at 3000—3500 (OH), 1740, 1245 (acetate), and 1700 cm.$^{-1}$ (11-ketone).

3β-*Acetoxyergost*-8-*en*-11-*one* (IX).—Thionyl chloride (0·05 c.c.) was added to 3β-acetoxy-9α-hydroxyergostan-11-one (20 mg.) in pyridine (0·3 c.c.) with external cooling. The solution was kept at 20° for 1 hr. and the steroid was then isolated with ether. The methanol solution of the product, when kept overnight, deposited needles of 3β-acetoxyergost-8-en-11-one, m. p. and mixed m. p. 138—140°, $[\alpha]_D$ +116°. The physical constants given in Part LXII (*loc. cit.*) are m. p. 138—140°, $[\alpha]_D$ +119°.

The authors are much indebted to Glaxo Laboratories Ltd. for gifts of materials and for financial assistance (to A. C.). Microanalyses were performed by Mr. E. S. Morton and Mr. H. Swift, and infra-red spectra were determined under the direction of Dr. G. D. Meakins.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 7th,* 1953.]

Studies in the Steroid Group. Part LXVI. Formation of Ergost-14-ene-3β : 5α-diol and Related Compounds.*

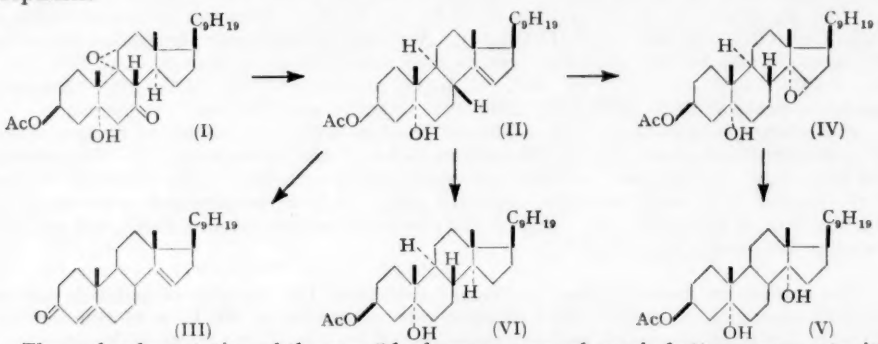
By PETER BLADON.

[Reprint Order No. 4706.]

Treatment of a 9α : 11α-epoxy-7-oxo-steroid with ethanedithiol and then Raney nickel led to the formation of a Δ^{14}-compound. This yielded an α-epoxide, reducible to a 14α-hydroxy-steroid.

IN an attempt to reduce the 9 : 11-epoxy-7-ketone (I) (Bladon, Henbest, Jones, Wood, Eaton, and Wagland, *J.*, 1953, 2916) to the corresponding 7-methylene compound, the ketone was treated first with ethanedithiol in the presence of perchloric acid (Hauptmann, *J. Amer. Chem. Soc.*, 1947, **69**, 562; Barton and Rosenfelder, *J.*, 1951, 1048). An uncrystallisable sulphur-containing product was obtained which, on treatment with Raney nickel, afforded a crystalline unsaturated compound in over 50% yield.

This new product has been shown to be 3β-acetoxyergost-14-en-5α-ol (II). The presence of the original 5α-hydroxyl group was indicated by acetylation (acetyl chloride) to a 3β : 5α-diacetate, and by hydrolysis followed by Oppenauer oxidation to give the unsaturated ketone (III). Infra-red and ultra-violet absorption measurements (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Bladon, Henbest, and Wood, *J.*, 1952, 2737) showed that the olefinic linkage was trisubstituted, and most probably situated at 9(11) or 14(15). A third, less likely possibility, 3β-acetoxyergost-7-en-5α-ol (Clayton, Henbest, and Jones, *J.*, 1953, 2015), could be ruled out in view of the difference in properties.



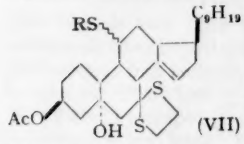
The molecular rotation of the new 5-hydroxy-compound was in better agreement with the 5α-hydroxy-Δ^{14}- than with the alternative $\Delta^{9(11)}$-structure (preceding paper; Barton and Klyne, *Chem. and Ind.*, 1948, 755), assuming little vicinal action between the double bond and the hydroxyl group. Monoperphthalic acid afforded an epoxide in good yield, the rotation change on formation of this epoxide being a small positive value ($M_D + 53°$) in contrast to the larger negative change ($M_D - 130°$) recorded for the formation of a 9α : 11α-epoxide (preceding paper). (These rotation differences are given in more detail below.) Furthermore, the new epoxide was reduced on treatment with lithium aluminium hydride in warm tetrahydrofuran, whereas 3β-acetoxy-9α : 11α-epoxyergostane was recovered unchanged (after reacetylation) when subjected to the same conditions (see also Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118; Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278). The original olefin is therefore the Δ^{14}-compound (II), and the epoxide is formulated as the 14α : 15α-compound (IV), and its lithium aluminium hydride reduction product as the 3β : 5α : 14α-triol, mild acetylation of which gives the 3β-monoacetate (V).

Hydrogenation of (II) readily afforded the saturated diol formulated as (VI), since Δ^{14}-compounds with 17β-side-chains give 14α-steroids on reduction (Ruzicka, Plattner,

* Part LXV, preceding paper.

Heusser, and Meier, *Helv. Chim. Acta*, 1947, **30**, 1342). The rotation of (VI) was in excellent agreement with the expected value (3β-acetoxyergostane + 3β-acetoxycholestan-5α-ol − 3β-acetoxycholestane).

In the absence of crystalline intermediates it is not easy to arrive at a detailed explanation for the formation of the Δ^{14}-compound from (I). However, it is likely that normal thioketal formation takes place at $C_{(7)}$, and that the 9 : 11-epoxide ring is opened affording a product with a thio-group at $C_{(11)}$ and a hydroxyl group at $C_{(9)}$. The latter group may be eliminated and the $\Delta^{8(9)}$-olefin isomerised to a Δ^{14}-olefin by the perchloric acid present. Products of structure (VII; $R = CH_2 \cdot CH_2 \cdot SH$) may thus be present in the non-crystalline thioketal, although sulphur analysis of this material indicated that other compounds containing less sulphur must also be present.



(VII)

Molecular rotation contributions of $\Delta^{9(11)}$- *and* Δ^{14}-*bonds.*

Average value for Δ^{14}-bond given by Barton and Klyne (*loc. cit.*)	+28
3β-Acetoxyergost-14-en-5α-ol (II) − 3β-acetoxyergostan-5α-ol (VI)	+32
3β-Acetoxyergost-9(11)-ene − 3β-acetoxyergostane	+58

Molecular rotation increments on formation of 9α : 11α- *and* 14α : 15α-*epoxides.*

Olefin	M_D, olefin	M_D, oxide	Δ	Ref.
3β-Acetoxyergost-14-en-5α-ol (II)	+ 37°	+ 90°	+ 53°	—
Methyl 3β-acetoxy*allo*eti-14-enate	+113	+124	+ 11	1
Methyl 3α : 12α-diacetoxychol-14-enate	+500	+515	+ 15	2
3β-Acetoxyergost-9(11)ene	+ 75	− 55	−130	3
3β-Acetoxy-22α-spirost-9(11)-ene	−246	−307	− 61	4
Methyl 3α-acetoxychol-9(11)-enate	+260	+188	− 72	5

References: **1**, Plattner, Ruzicka, Heusser, Pataki, and Meier, *Helv. Chim. Acta*, 1946, **29**, 942, 2033. **2**, Plattner, Ruzicka, and Holtermann, *ibid.*, 1945, **28**, 1660. **3**, Preceding paper. **4**, Djerassi, Martinez, and Rosenkranz, *loc. cit.* **5**, Fieser and Rajagopalan, *loc. cit.*

Experimental

General experimental directions are as given in Part LXI, *J.*, 1953, 2916.

Reaction of 3β-*Acetoxy*-9α : 11α-*epoxy*-7-*oxoergostan*-5α-*ol with Ethanedithiol.*—A solution of the steroid (1·4 g.) in dioxan (5 c.c.) and ethanedithiol (2·15 g.; Owen and Smith, *J.*, 1951, 2973) containing 60% perchloric acid (0·3 c.c.) was kept at 20° for 2 days. Crystals which separated at first were redissolved by gentle warming. The mixture was diluted with ether and washed thrice with aqueous potassium hydroxide (2%) and twice with water, dried, and evaporated to a glassy residue (1·51 g.). This could not be crystallised (Found: S, 13·6%).

3β-*Acetoxyergost*-14-*en*-5α-*ol* (II).—The crude thioketal (1·3 g.) was heated under reflux for 9 hr. with Raney nickel (15 c.c. of sludge) and dioxan (80 c.c.). The nickel was filtered off and washed with chloroform, and the filtrates evaporated to a solid residue (1·1 g.). This was acetylated overnight at 20° in the usual way, and the product (in benzene) was chromatographed on alumina (70 g.). Benzene–ether (4 : 1) (750 c.c.) eluted a solid fraction (780 mg.), which when crystallised from methanol gave material (620 mg.), m. p. 152—156°. Another crystallisation afforded 3β-*acetoxyergost*-14-*en*-5α-*ol* as plates, m. p. 158—161°, $[\alpha]_D$ +8° (*c*, 1·07) (Found: C, 78·5; H, 10·95. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). Infra-red spectrum: peaks at 3500 (OH), 1730, 1700, 1250 (acetate), 818 cm.$^{-1}$ (Δ^{14}); (in $CHCl_3$) acetate bands at 1715 and 1250 cm.$^{-1}$.

Alkaline hydrolysis of this acetate gave *ergost*-14-*ene*-3β : 5α-*diol* (plates from methanol), m. p. 215—225°, $[\alpha]_D$ +10° (*c*, 0·38) (Found: C, 79·4; H, 11·6. $C_{28}H_{48}O_2,\frac{1}{2}CH_3 \cdot OH$ requires C, 79·1; H, 11·6%). 3β : 5α-*Diacetoxyergost*-14-*ene* was obtained by heating a mixture of the 3-acetate (100 mg.), chloroform (5 c.c.), acetyl chloride (4 c.c.), and dimethylaniline (6 c.c.) for 18 hr. Isolation with ether gave a gum (140 mg.), which even after chromatography failed to crystallise. It was therefore distilled, b. p. 170—180° (bath)/10^{-5} mm., $[\alpha]_D$ +41° (*c*, 0·62) (Found: C, 77·1; H, 10·4. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·5%). Infra-red spectrum: peaks at 1737 and 1250 cm.$^{-1}$ (acetate). This partly solidified but the crystals (m. p. 85—90°) could not be recrystallised from a solvent.

Ergosta-4 : 14-*dien*-3-*one* (III).—The above 3 : 5-diol (120 mg.), dry acetone (3 c.c.), aluminium *tert.*-butoxide (0·75 g.), and toluene (5 c.c.) were heated under reflux for 3 hr., the product then being isolated with ether. The oily material (135 mg.) obtained was distilled

twice, b. p. 190—205° (bath)/10^{-5} mm., yielding a pale yellow oil ($\lambda_{max.}$ 2400 Å; ε 12,500) which solidified. Three crystallisations from methanol gave the *ketone* (12 mg.), m. p. 118—120° (Found: C, 83·5; H, 10·95. $C_{28}H_{44}O,\frac{1}{2}CH_3{\cdot}OH$ requires C, 83·0; H, 11·2%); $\lambda_{max.}$ (in EtOH) 2400 Å; ε 16,000. The 2 : 4-*dinitrophenylhydrazone* (crystallised from ethyl acetate) had m. p. 237—240° (Found: C, 70·45; H, 8·4; N, 10·35. $C_{34}H_{48}O_4N_4$ requires C, 70·8; H, 8·4; N, 9·7%); $\lambda_{max.}$ (in $CHCl_3$) 2610, 2930, 3930 Å; ε 19,000, 11,700, and 31,200 respectively.

3β-*Acetoxyergostan-5α-ol* (VI).—3β-Acetoxyergost-14-en-5α-ol (118 mg.) was shaken with pre-reduced Adams catalyst (50 mg.) in glacial acetic acid (12·5 c.c.) in hydrogen until absorption ceased (7·4 c.c. at 22°/761 mm.; calc., 6·5 c.c.). After removal of the catalyst and evaporation, 3β-*acetoxyergostan-5α-ol* crystallised from ethyl acetate as plates, m. p. 204—207° (change of form at 200°), $[\alpha]_D$ +1° (*c*, 0·87) (Found: C, 78·2; H, 11·6. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%). Infra-red spectrum: peaks at 3450 (OH); 1734, 1702, 1260 cm.$^{-1}$ (acetate). Hydrolysis yielded *ergostane*-3β : 5α-*diol*, m. p. 237—244° (anisotropic liquid >200°), $[\alpha]_D$ +8° (*c*, 0·46) (Found, in material sublimed at 200°/10^{-6} mm.: C, 80·7; H, 11·95. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·05%).

3β-*Acetoxy*-14α : 15α-*epoxyergostan-5α-ol* (IV).—The Δ^{14}-compound (250 mg.) in dioxan (3 c.c.) was treated with monoperphthalic acid (4 c.c. of 0·65N-solution in ether), and the solution kept at 20° overnight. Isolation with ether followed by 2 crystallisations from methanol yielded the *epoxide* (97 mg.) as plates, m. p. 161—163° $[\alpha]_D$ +19° (*c*, 1·17) (Found: C, 76·05; H, 10·55. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). A second crop (120 mg.), m. p. 158—161°, was also obtained. The compound was transparent in the 2000—2200-Å region and gave no colour with tetranitromethane.

3β-*Acetoxyergostane-5α* : 14α-*diol* (V).—The epoxide (70 mg.), lithium aluminium hydride (250 mg.), and purified tetrahydrofuran (12·5 c.c.) were heated under reflux for 8 hr. After addition of ethyl acetate and dilute hydrochloric acid, the product was isolated with ether–chloroform and acetylated overnight in the usual way. Crystallisation from ethanol–methanol gave the 5α : 14α-*diol* as fine needles, m. p. 239—241° (change of form near 200°), $[\alpha]_D$ −5° (*c*, 0·7) (Found, on material sublimed at 200°/10^{-6} mm.: C, 75·4; H, 10·9. $C_{30}H_{52}O_4$ requires C, 75·6; H, 11·0%). Infra-red spectrum: peaks at 3210 (OH), 1735 and 1265 cm.$^{-1}$ (acetate). Lithium aluminium hydride in boiling ether for 1 hr. did not reduce the epoxide.

The author thanks Professor E. R. H. Jones, F.R.S., and Dr. H. B. Henbest for their advice and interest in this work, which was carried out during the tenure of an I.C.I. Fellowship. He is also indebted to Glaxo Laboratories Ltd. for gifts of materials, to Mr. E. S. Morton, Mr. H. Swift, and Mr. G. Wood for microanalyses, and to Dr. G. D. Meakins, Mrs. D. Hallan, and Miss W. Peadon for the infra-red spectra.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 7th*, 1953.]

Some Surface Properties of Docosyltrimethylammonium Bromide, and of Docosane-1-sulphonic Acid and its Sodium Salt.

By F. G. HOLLIMAN, J. F. LARGIER, and F. SEBBA.

[Reprint Order No. 4716.]

The effect of docosyltrimethylammonium bromide, and docosane-1-sulphonic acid and its sodium salt on the rate of evaporation of a water substrate has been investigated and the effect of the sulphonic acid found to be appreciable.

AVAILABLE evidence suggests that, for a monolayer spread on water to be effective in reducing the rate of evaporation of the substrate appreciably, it must consist of an unbranched long-chain hydrocarbon and a strongly polar, small head group, and be compressed to the condensed phase. So far, the longest hydrocarbon chain investigated has been that in docosanol (Sebba and Briscoe, *J.*, 1940, 106). Longer chains could not easily be investigated as the alcohols and acids of higher homologues do not spread easily. In the search for a spontaneously spreading substance that would form a monolayer which, without external compression, would have an appreciable effect on the rate of evaporation of water from open surfaces, it was decided to investigate the long-chain sulphonic acids and their salts, whose surface properties have not yet been examined. These substances

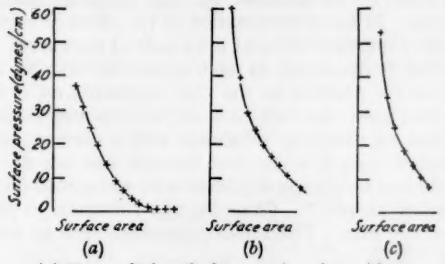
show considerable surface activity up to C_{18}, but molecules of this length are too soluble in water to give a durable monolayer. As a preliminary, a C_{22} sulphonic acid and its salt and the C_{22} quaternary ammonium salt have been synthesised and investigated.

Experimental

Erucic acid from rape-seed oil (*Org. Synth.*, Coll. Vol. II, p. 258) was esterified, and the ester reduced (Adams's catalyst) to ethyl behenate. This, by a modified Bouveault–Blanc reaction, butanol being used in place of ethanol, yielded docosan-1-ol. The corresponding bromide when heated with sodium sulphite at 200° (Strecker, *Annalen*, 1873, **168**, 145; Reed and Tartar, *J. Amer. Chem. Soc.*, 1935, **57**, 570) afforded *sodium docosane-1-sulphonate* which separated from ethanol as a white crystalline solid (Found: C, 64·3; H, 11·1. $C_{22}H_{45}O_3SNa$ requires C, 64·2; H, 10·9%). It is insoluble in cold water but soluble in hot water, from which it is precipitated on cooling in either crystalline or gelatinous form; it is practically insoluble in hexane, benzene, ether, or chloroform.

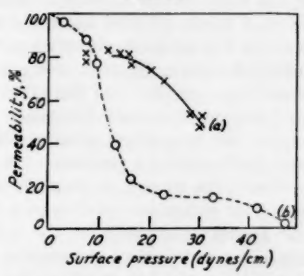
Dry hydrogen chloride was bubbled into a suspension of the sodium salt in benzene, heated under reflux, to liberate docosane-1-sulphonic acid. After 2 hr. the residual solid was filtered

Fig. 1.



(*a*) Docosyltrimethylammonium bromide.
(*b*) Docosane-1-sulphonic acid.
(*c*) Sodium docosane-1-sulphonate.

Fig. 2.



(*a*) Docosane-1-sulphonic acid.
(*b*) Docosan-1-ol.

off, and the filtrate shaken twice with water to remove hydrochloric acid; the layers were separated by centrifuging. Removal of the benzene by distillation under reduced pressure left a white, waxy solid, easily decomposed by heat (even at 60—70° *in vacuo*), moderately soluble in hexane and benzene. It is insoluble in cold water, but when heated forms a clear solution from which it sets to a gel on cooling.

When heated with trimethylamine at 100° for 24 hr. in a sealed tube, docosyl bromide was converted into docosyltrimethylammonium bromide (*J. Biol. Chem.*, 1924, **59**, 905) which was recrystallised several times from acetone–ethanol. The solid decomposes below its m. p. (Found: C, 67·1; H, 12·2. Calc. for $C_{25}H_{54}NBr$: C, 66·9; H, 12·1%).

The surface-pressure–area curves were determined in the usual way, by means of a Langmuir–Adam trough and a floating-barrier surface balance. The change in resistance to evaporation with change of surface pressure was measured by Sebba and Sutin's method (*J.*, 1952, 2513).

Results.—The most satisfactory solvent from which to spread the docosyltrimethylammonium bromide was chloroform. Being denser than water, the chloroform had to be placed on the surface very carefully in which case a satisfactory film could be obtained, which on distilled water had an equilibrium pressure of 28·4 dynes/cm. Owing to the slight solubility of the monolayer, the absolute values of the area occupied per molecule could not be determined, and Fig. 1 (*a*), only shows the shape of the *F–A* curve. At pressures above 30 dynes/cm. the solubility of the film was so great that no reliable measurements could be made. For the same reason, it was not possible to determine the effect on evaporation at high pressures. At a surface pressure of 23 dynes/cm., the permeability was found to be 97%, and at 27 dynes to be 87%. The resistance to evaporation offered by this film, even when condensed, is therefore, not very marked.

Sodium docosane-1-sulphonate is insoluble in all common organic solvents except ethyl alcohol. In spite of the obvious disadvantages of a soluble polar solvent, there was no alternative to spreading it from a hot solution in ethyl alcohol, to which sufficient benzene had been added to make the solution partially immiscible with water, but not enough to precipitate the salt. It was difficult to study the surface characteristics of this substance satisfactorily, as owing

to solubility, the surface pressures were never steady, but decreased continuously, a phenomenon noticed with some other films by Sebba and Briscoe (*J.*, 1940, 114). A pseudo-equilibrium pressure of 30 dynes/cm. was obtained. Even a substrate containing Ba^{++} ions did not depress the solubility, in spite of the fact that barium sulphonates are generally less soluble. This difficulty made determination of an exact *F–A* curve impracticable, therefore Fig. 1(*c*) shows only the general shape of the curve. Nor could a complete study be made of the change of evaporation through the film with change in pressure. However, at an approximate surface pressure of 20 dynes/cm., the permeability was found to be 72%, and at 28 dynes/cm. it was 54%. This indicates that at pressures in excess of 28 dynes/cm., the resistance to evaporation offered by the monolayer would be considerable.

Docosane-1-sulphonic acid is soluble in benzene, and was, therefore, spread from a benzene solution. It is unfortunate that as the sulphonic acids are relatively strong, the possibility of slight contamination with the sodium salt which is slightly soluble in benzene could not be entirely excluded. This monolayer also showed slight solubility, as indicated by the fall of surface pressure with time. A pseudo-equilibrium pressure of approximately 11 dynes/cm. was found, but the true equilibrium surface pressure may be somewhat greater. The monolayer appeared to be an elastic solid at that pressure. Again, owing to the solubility of the monolayer, the value of the molecular cross-section could not be obtained, but only the general shape of the *F–A* curve, plotted against a relative area. In the determination of the effect of surface pressure on the rates of evaporation, the solubility imposed limits at both ends of the curve. It prevented determinations at pressures higher than 30 dynes/cm. as the film was too unstable and dissolved too rapidly. On the other hand, since the pressure in the film represents an equilibrium between dissolved substance and its monolayer, the reduction of the pressure below 7 dynes/cm. led to gradual penetration of the film by dissolved substance with a corresponding increase in the surface pressure. It can be stated unequivocally that this rise was not due to impurities in the trough, as no such rise was observed before the sulphonic acid was spread on the water. The substrate used was a borate buffer at pH 7. Changing the substrate to pH 2 had no appreciable effect on the solubility of the film. The relation between rate of water permeability and surface pressure is shown in Fig. 2.

It will be noticed that, when the surface pressure is increased beyond 17 dynes/cm., there is a marked reduction in rate of water evaporation. A puzzling feature, however, is that the permeability appears to be relatively constant at 80% between pressures of 7 and 17 dynes/cm., whereas it would be expected to rise steadily towards 100% permeability [the continuous line (*a*) in Fig. 2 should be continued to the left]. This is not an obvious experimental error, as the experiment was repeated, though the possibility of a small amount of a more impenetrable impurity in the monolayer cannot be excluded. A similar plateau, though associated with much more marked evaporation resistance, is shown by docosan-1-ol, and its curve (taken from Sebba and Briscoe's paper, *loc.cit.*) is shown, for comparison, in Fig. 2 as broken lines. If the phenomenon is real, it would be profitable to synthesise a similar acid with two or more additional carbon atoms in the chain, for the solubility effect should then be less serious.

The Table summarises the relative effect on permeability of various monolayers of approximately the same chain length at approximately the same surface pressures.

Compound	Surface pressure, dynes/cm.	Permeability, %
Docosyltrimethylammonium bromide	27	87
Sodium docosane-1-sulphonate	28	54
Docosane-1-sulphonic acid	28	55
Arachidic acid *	28	31
Docosan-1-ol *	28	15

* Sebba and Briscoe (*J.*, 1940, 106).

From these results it is seen that the order of effectiveness of the end group is $OH > CO_2H > SO_3^- > NMe_3^+Br^-$. The sodium docosane-1-sulphonate seems to have a resistance to evaporation similar to that of the free acid, as is to be expected, for the long-chain anions are identical and the sulphonic acids are relatively strong. The sodium salt has the advantage of a higher equilibrium pressure, so it offers indications that a self-spreading surface-active substance, which will attain of its own accord a surface pressure large enough appreciably to reduce evaporation from open water surfaces, may be found amongst the sodium salts of the sulphonic acids of slightly greater chain-length than the one used in these experiments.

Department of Chemistry, University of Cape Town. [*Received, October 12th*, 1953.]

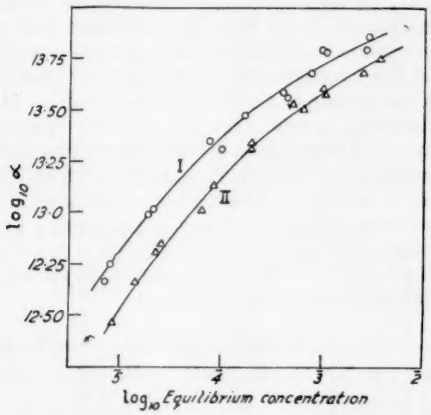
Adsorption of Ions by Carborundum.

By G. A. H. Elton and J. W. Mitchell.

[Reprint Order No. 4739.]

Measurements of the extent of ion adsorption by carborundum from some dilute electrolyte solutions have been made conductometrically, and the results have been used to calculate the energies of adsorption of the individual ions.

Benton and Elton (*Trans. Faraday Soc.*, 1953, **49**, 1213) have shown that for a non-ionogenic surface it is possible to use the results of measurements of adsorption from electrolyte solutions to calculate the energies of adsorption of individual ions, provided that the appropriate electrokinetic charges and potentials are known. This paper gives the results of measurements of adsorption by carborundum, the conductance-loss method described by Benton and Elton (*loc. cit.*) being used, and the calculated adsorption energies for six univalent ions.



I, HCl.
II, HNO_3

Solutions of hydrochloric and nitric acids undergo a marked decrease in conductivity on equilibration with a large area of carborundum. The figure shows the values of $\log_{10} \alpha$, the number of solute ions in excess per square cm. in the whole double layer, for these solutions. The number, n_i^D, of ions of type i in excess in the diffuse part of the layer can be calculated from the equilibrium bulk concentrations (n_i^B ions per ml.) and the corresponding electrokinetic potential ζ, Grahame's equation (*Chem. Reviews*, 1947, **41**, 441) being used, *viz.*,

$$n_i^D = -2\lambda n_i^B[1 - \exp(-z_i e\zeta/kT)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where λ is the Debye–Huckel expression for the effective double layer thickness, z_i is the number of electronic charges, e, carried by the ion of type i, k is the Boltzmann constant, and T is the absolute temperature. The number of solute ions of each type in the diffuse layer was calculated by using values of ζ given by Elton and Mitchell (*J.*, 1953, 3690). The corresponding number in the fixed layer, n_i^F, was then obtained from the equation

$$n_i^F = \alpha_i - n_i^D \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

As shown by Benton and Elton (*loc. cit.*), the values of n_{anion}^F obtained in this way are final, but the values of n_H^F represent only first approximations to the number of adsorbed hydrogen ions, since the conductometric method does not directly detect adsorption of ions produced by the dissociation of the solvent, and the fixed layer will contain an initially unknown number of hydroxyl ions, and an equal additional number of hydrogen ions.

The energy of adsorption per g.-ion of a species of type i is given by

$$E_i = \boldsymbol{R}T \log_e n_i^{\mathrm{F}}/n_i^{\mathrm{B}} + z_i \boldsymbol{F}\zeta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $\boldsymbol{F}$ is the Faraday equivalent. The values of the adsorption energies of the chloride and nitrate ions, together with the first-approximation values for the hydrogen ion, calculated in this way, are given in Table 1.

TABLE 1. *Adsorption energies (in kcal.), from results in acid solutions.*

Normality	E_{H}*	E_{Cl}	E_{H}*	$E_{\mathrm{NO_3}}$	Normality	E_{H}*	E_{Cl}	E_{H}*	$E_{\mathrm{NO_3}}$
1×10^{-5}	−6·8	−1·44	−6·9	−1·95	2×10^{-4}	−7·0	−2·81	−7·0	−3·07
2×10^{-5}	−6·7	−1·66	−6·8	−2·05	5×10^{-4}	−7·2	−3·39	−7·2	−3·57
5×10^{-5}	−6·8	−2·01	−6·9	−2·40	1×10^{-3}	−7·3	−3·83	−7·4	−3·96
1×10^{-4}	−6·9	−2·40	−6·9	−2·71	2×10^{-3}	−7·7	−4·29	−7·6	−3·29

* First approximation only.

Solutions of potassium chloride, potassium nitrate, and sodium chloride show an increase in conductivity on equilibration with a large area of carborundum. However, the electrokinetic charge is greater in these solutions than in the acid solutions (Elton and Mitchell, *loc. cit.*), so that considerable adsorption must in fact occur. The rise in conductivity was attributed to the fact that hydrogen ions are released from the diffuse layer, owing to the decrease in electrokinetic potential caused by the presence of the salt; since the mobility of the hydrogen ion is much greater than that of any of the solute ions in the salt solutions, the release of a relatively small number of hydrogen ions could produce an increase in conductivity greater than the decrease caused by the adsorption of solute ions. On this basis, using the values for the adsorption energies of the solute anions at the appropriate concentrations, obtained from the work on acid solutions, we can calculate the numbers of ions of each type adsorbed into the fixed layer, Benton and Elton's (*loc. cit.*) method of successive approximations being used. The values for the adsorption energy of the hydrogen ion used in this calculation are the first-approximation values obtained as described above. The adsorption energies for the sodium and potassium ions, obtained in this way, are given in Table 2.

TABLE 2. *Adsorption energies (in kcal.), from results in salt solutions.*

Normality	E_{K}(KCl)	E_{K}(KNO_3)	E_{Na}(NaCl)	Normality	E_{K}(KCl)	E_{K}(KNO_3)	E_{Na}(NaCl)
1×10^{-5}	−6·4	−6·4	−6·5	2×10^{-4}	−6·9	−6·9	−6·8
2×10^{-5}	−6·6	−6·6	−6·4	5×10^{-4}	−7·1	−7·1	−7·0
5×10^{-5}	−6·6	−6·6	−6·5	1×10^{-3}	−7·3	−7·2	−7·2
1×10^{-4}	−6·8	−6·7	−6·6	2×10^{-3}	−7·4	−7·5	−7·4

Elton and Mitchell (*loc. cit.*) have shown that the electrokinetic charge on a carborundum surface in water of high purity is very small, and tends towards zero as the amount of electrolyte impurities in the water is reduced. It therefore appears reasonable to assume that carborundum takes up its charge entirely by ion adsorption, and not by surface ionisation, *i.e.*, we may write

$$\sigma_1 = -\sigma_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where σ_1 is the charge in the fixed layer, and σ_2 that in the diffuse layer, measured in electrokinetic experiments. Furthermore

$$\Sigma z_i e n_i^{\mathrm{F}} = \sigma_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

It is found that in order to satisfy equation (5), it is necessary to assume the adsorption of a fairly large number of anions from the solvent. Assuming (see Benton and Elton, *loc. cit.*) that all of the anions adsorbed from conductivity water are hydroxyl ions (*i.e.*, neglecting bicarbonate and other ions), we can obtain $n_{\mathrm{OH}}^{\mathrm{F}}$ from equation (5), and hence, using equation (3), obtain a value of E_{OH}. This value will be only a first approximation, in view of the use of the approximate value of E_{H}. The hydroxyl-ion concentrations in the salt solutions are similar to those in the more dilute acid solutions, and the first-approximation values of E_{OH} interpolated at appropriate concentrations may be used to

obtain first estimates of n^{p}_{OH} in the most dilute acid solutions. Hence we obtain second-approximation values of n^{p}_{H}, given by

$$(n^{p}_{H})_2 = (n^{p}_{H})_1 + (n^{p}_{OH})_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $(n^{p}_{H})_1$ and $(n^{p}_{H})_2$ are respectively the first and second approximations to n^{p}_{H}, and $(n^{p}_{OH})_1$ is the first approximation to n^{p}_{OH}. $(n^{p}_{H})_2$ may then be used in equation (3) to obtain a second approximation to E_H, which can be used in turn in the calculation for the salt solutions. The system of successive approximations is continued until constant values of E_H and E_{OH} are obtained. It may be noted that the calculated values of the adsorption energies of the cation and anion from the salt are not affected in this process.

Tables 3 and 4 summarise the results obtained for the salt solutions and for the more dilute acid solutions. It is not possible to perform the complete calculation indicated

TABLE 3. *Final results for dilute acid solutions.*

Normality	Acid	$n^{p}_{H} \times 10^{-13}$, ions/cm.^{2}	$n^{p}_{OH} \times 10^{-13}$, ions/cm.^{2}	E_H, kcal.	E_{OH}, kcal.
1×10^{-5}	HCl (1)	2·2	1·7	−5·9	4·8
	HCl (2)	1·5	1·0	−6·2	4·5
	HNO_3	1·2	0·9	−6·1	4·3
2×10^{-5}	HCl (1)	2·5	1·6	−6·1	5·1
	HCl (2)	2·0	1·1	−6·3	4·8
	HNO_3	1·7	1·1	−6·3	4·7
5×10^{-5}	HCl (1)	2·5	0·9	−6·6	5·1
	HCl (2)	2·2	0·6	−6·6	4·9
	HNO_3	2·5	0·8	−6·4	5·2

HCl (1), from combination of results for HCl and KCl.
HCl (2), from combination of results for HCl and NaCl.
HNO_3, from combination of results for HNO_3 and KNO_3.

TABLE 4. *Final results for salt solutions.*

Normality	Salt	$n^{p}_{OH} \times 10^{-13}$, ions/cm.^{2}	$n^{p}_{H} \times 10^{-13}$, ions/cm.^{2}	E_H, kcal.	E_{OH}, kcal.
2×10^{-5}	KCl	1·5	1·8	−5·9	4·5
	NaCl	1·0	1·2	−6·1	4·4
	KNO_3	1·1	1·1	−6·0	4·2
2×10^{-4}	KCl	1·4	2·8	−6·2	5·1
	NaCl	1·1	2·1	−6·3	4·9
	KNO_3	1·0	1·9	−6·3	4·7
2×10^{-3}	KCl	0·7	3·6	−6·4	5·1
	NaCl	0·7	2·6	−6·4	4·9
	KNO_3	0·8	3·5	−6·5	5·2

above for acid solutions of concentrations of 1×10^{-4}N and above, for the values of n^{B}_{OH} in these solutions are lower than those obtained in any of the salt solutions. However, as the acid concentration rises, n^{p}_{OH} falls, and eventually will become negligible with respect to n^{p}_{H}, in which case the first-approximation value of E_H will be equal to the final value. In order to obtain the final interpolated values of E_H given in Table 5, we have assumed that this is the case in the most concentrated acid solutions studied, *viz.*, 2×10^{-3}N. It is possible, therefore, that the value of −7·6 kcal. taken at this concentration is slightly low (too negative), but it is considered unlikely that hydroxyl-ion adsorption is at all significant at such concentrations.

TABLE 5. *Adsorption energy of the hydrogen ion (final values).*

Normality	1×10^{-5}	2×10^{-5}	5×10^{-5}	1×10^{-4}	2×10^{-4}	5×10^{-4}	1×10^{-3}	2×10^{-3}
E_H, kcal.	−6·1	−6·2	−6·5	−6·7	−6·9	−7·2	−7·4	−7·6

As seen from Table 2, the values of E_K obtained from potassium chloride and from potassium nitrate are in agreement to $\pm$0·1 kcal. over the whole concentration range. The agreement between values of E_H calculated from different systems is slightly less close, but is very satisfactory, bearing in mind the assumptions involved, and the indirect method of calculation necessary. There is little difference between the energies for sodium

and potassium ions, E_{Na} being generally slightly higher (more positive). The energies for these ions, and for the hydrogen ion, are roughly 1 kcal. higher for carborundum than for silica (Benton and Elton, *loc. cit.*). E_{Cl} and E_{NO_3} for carborundum are very similar to the corresponding values for silica, and it is possible that for these ions, adsorption on the two solids occurs on sites of similar type.

Experimental

100-Mesh carborundum powder, supplied by the Carborundum Co., Ltd., was cleaned as described by Elton and Mitchell (*loc. cit.*), and freed from any fine material by washing and decantation. The surface area per g. ($1{\cdot}01 \times 10^3$ cm.^{2}) was determined, and the electrolytes used were purified, by the methods of Dulin and Elton (*J.*, 1952, 286). Conductivity water was prepared by the ion-exchange method; its conductivity was usually 0·2—0·3 gemmho, and was always less than 0·5 gemmho. Benton and Elton (*J.*, 1953, 2096) have shown that water so prepared is suitable for use in electrokinetic experiments.

Apparatus and experimental technique were as described by Benton and Elton (*Trans. Faraday Soc., loc. cit.*). Addition of carborundum to water was found to produce a rise in conductivity, proportional to the area/volume ratio (θ), and equal to $2{\cdot}0 \times 10^{-9}$ ohm^{-1} cm.$^{-1}$ θ^{-1}; this was ascribed to the dissolution of a surface layer on the carborundum (cf. a similar effect for silica), giving colloidal particles with hydrogen gegen-ions. Blank conductivity runs in water previously equilibrated with a large area of carborundum showed that the conductivity of the dissolved material was additive to that of dissolved acids and salts, but was largely suppressed by dissolved alkali.

All experiments were carried out at $25{\cdot}00° \pm 0{\cdot}01°$.

Battersea Polytechnic, London, S.W.11 [*Received, October 21st,* 1953.]

Reactions of Methyl α-D-*Mannoside with Aldehydes.*

By John Honeyman and J. W. W. Morgan.

[Reprint Order No. 4769.]

The condensations of acetaldehyde, propaldehyde, and benzaldehyde with methyl α-D-mannoside give fully substituted compounds as the main products. However, a method is described for the preparation of methyl 4 : 6-*O*-ethylidene-α-D-mannoside.

In contrast with methyl α-D-glucoside and α-D-galactoside, which are readily converted into the 4 : 6-*O*-benzylidene compounds, the α-D-mannoside reacts with benzaldehyde at 150° to give a complex mixture from which Robertson (*J.*, 1934, 330) isolated one methyl 4 : 6-*O*-benzylidene-α-D-mannoside and two isomeric 2 : 3-4 : 6-di-*O*-benzylidene derivatives. By shaking the mannoside at room temperature with paraldehyde containing concentrated sulphuric acid, propaldehyde and concentrated hydrochloric acid, or benzaldehyde and zinc chloride, one isomer of each of the fully substituted di-*O*-ethylidene, di-*O*-propylidene, and di-*O*-benzylidene derivatives has now been prepared. Similar reactions of methyl α-D-glucoside with paraldehyde or propaldehyde give, by contrast, the methyl 4 : 6-*O*-alkylidene-2 : 3-oxydialkylidene-α-D-glucoside. The di-*O*-alkylidenemannosides contain no free hydroxyl groups, as they are recovered unchanged when their nitration by Honeyman and Morgan's general method (*Chem. and Ind.*, 1953, 1035) is attempted. By using a short reaction time it has been possible to prepare, reasonably, methyl 4 : 6-*O*-ethylidene-α-D-mannoside. This was difficult to purify to analytical standard because it separated from suitable solvents as a jelly, from which the last traces of solvent were difficult to remove. It was shown, nevertheless, to be a very pure single compound by its conversion in high yield into its crystalline diacetate, dinitrate, ditoluene-*p*-sulphonate, and dimethyl ether, and its regeneration in the same form from its diacetate. The specified structure was determined by methylation, hydrolysis, and benzoylation to methyl 2 : 3-di-*O*-methyl-α-D-

mannoside 4 : 6-dibenzoate, previously prepared by Robertson (*loc. cit.*). Methyl 2 : 3-4 : 6-di-*O*-ethylidene-α-D-mannoside was readily hydrolysed to methyl α-D-mannoside, but the mono-ethylidene derivative was not isolated in this reaction.

Experimental

Solvents were evaporated at reduced pressure.

Methyl α-D-Mannoside.—This was prepared from carob gum by Smith's method (*J.*, 1948, 1989). The average yield was lower than that obtained by Smith.

Methyl 4 : 6-O-Ethylidene-α-D-mannoside and Methyl 2 : 3-4 : 6-Di-O-ethylidene-α-D-mannoside.—Finely ground methyl α-D-mannoside (20 g.) was shaken at room temperature with paraldehyde (200 ml.), containing concentrated sulphuric acid, until all the solid had dissolved (about 30 min.). Acid was neutralised with anhydrous potassium carbonate, and the mixture then filtered. Evaporation of the filtrate gave a syrup which solidified when shaken with water (150 ml.). The solid was collected, dried (14 g., 55%), and recrystallised from aqueous alcohol or light petroleum, forming soft needles of *methyl 2 : 3-4 : 6-di-O-ethylidene-α-D-mannoside*, m. p. 72°, $[\alpha]_D^{19}$ +14·2° (*c*, 1·0 in $CHCl_3$) (Found: C, 53·8; H, 7·3; CH_3·CHO, 36·2. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·3; CH_3·CHO, 35·8%). The aqueous filtrate was evaporated to a white solid which, recrystallised from carbon tetrachloride, was *methyl 4 : 6-O-ethylidene-α-D-mannoside* (7·1 g., 31%), m. p. 117°, $[\alpha]_D^{20}$ +77° (*c*, 1·0 in $CHCl_3$) (Found: C, 50·0; H, 7·8. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3%).

In a similar experiment, with a longer reaction time, only the di-*O*-ethylidene compound was obtained.

Estimation of Acetaldehyde.—The ethylidene content of the fully substituted mannoside was estimated by an adaptation of Ripper's method (see Wild, "Estimation of Organic Compounds," University Press, Cambridge, 1953, p. 151) for determining acetaldehyde. A suspension of the compound was gently distilled with 3% sulphuric acid into an ice-cooled flask. The acetaldehyde was estimated by adding aqueous sodium hydrogen sulphite and titrating the excess with iodine. As a control experiment the ethylidene content of methyl 4 : 6-*O*-ethylidene-2 : 3-*O*-oxydiethylidene-α-D-glucoside was determined (Found: CH_3·CHO, 44·6. $C_{13}H_{22}O_7$ requires CH_3·CHO, 45·5%).

Characterization of Methyl 4 : 6-O-Ethylidene-α-D-mannoside.—Silver oxide (10 g.) was added in 1-g. portions during 5—6 hr. to methyl 4 : 6-*O*-ethylidene-α-D-mannoside (3 g.) in boiling methyl iodide (20 ml.). After the suspension had boiled for 18 hr. more the silver residue was filtered off and washed with methanol, and the washings and filtrate combined and evaporated. Two such treatments were necessary for complete methylation. The crystalline product (2·94 g., 87%) was purified by chromatography in benzene solution through alumina, yielding large prisms of *methyl 4 : 6-O-ethylidene-2 : 3-di-O-methyl-α-D-mannoside*, m. p. 42—44°, $[\alpha]_D^{18}$ +65·8° (*c*, 0·48 in $CHCl_3$) (Found: C, 53·4; H, 8·1. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1%).

This compound (1 g.), Amberlite ion-exchange resin IR 120 (H) (1 g.), and water (20 ml.) were heated on a steam-bath for 4½ hr. The resin was filtered off and the filtrate was concentrated to a syrup, a solution of which in pyridine (5 ml.) was mixed with benzoyl chloride (1·5 ml.) in pyridine (5 ml.) at 0°. After 90 min., water (1 ml.) was added dropwise, and 30 min. later the solution was poured into aqueous potassium carbonate at 0°. Dissolution of the resulting solid (1·23 g.) in a small amount of ether followed by cooling to 0° gave methyl 2 : 3-di-*O*-methyl-α-D-mannoside 4 : 6-dibenzoate (0·70 g., 40%), $[\alpha]_D^{17}$ +50·2° (*c*, 1·2 in $CHCl_3$). This compound when first obtained melted at 101—102°, resolidified, and melted again at 120—121°, but a mixture with an authentic specimen prepared by Robertson (*loc. cit.*), m. p. 120—121°, $[\alpha]_D$ +52·9°, had m. p. 120—121°. Subsequent recrystallizations gave only the higher-melting form.

Acid Hydrolysis of Methyl 2 : 3-4 : 6-Di-O-ethylidene-α-D-mannoside.—Crude methyl 2 : 3-4 : 6-di-*O*-ethylidene-α-D-mannoside (40 g.) was boiled in water (100 ml.) with Amberlite ion-exchange resin IR 120 (H) (8 g.). When the compound had dissolved (4—5 hr.) the resin was filtered off and the filtrate concentrated. Extraction of the residue with carbon tetrachloride and concentration of the extract gave no methyl 4 : 6-*O*-ethylidene-α-D-mannoside. The residue, recrystallized from methanol, gave methyl α-D-mannoside (20·6 g., 65%), m. p. 188—189°.

Methyl 4 : 6-O-Ethylidene-α-D-mannoside 2 : 3-Diacetate.—Methyl 4 : 6-*O*-ethylidene-α-D-mannoside (5 g.), sodium acetate (1·5 g.), and acetic anhydride (15 g.) were heated on a steam-bath for 1 hr., and the mixture was then poured into ice–water (50 ml.). Recrystallization of the crude product from light petroleum gave slender needles (74%) of *methyl 4 : 6-O-ethylidene-α-D-*

mannoside 2 : 3-*diacetate*, m. p. 132°, $[\alpha]_D^{22}$ +36·7° (*c*, 1·0 in $CHCl_3$) (Found: C, 51·3; H, 6·2. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·6%).

Deacetylation of this compound (0·5 g.), in methanol (20 ml.) containing sodium (0·01 g.), gave a solid which recrystallized from carbon tetrachloride as jelly-like, very fine needles of methyl 4 : 6-*O*-ethylidene-α-D-mannoside (0·24 g., 69%), m. p. 114°, $[\alpha]_D^{19}$ +74° (*c*, 1·0 in $CHCl_3$).

Methyl 4 : 6-O-*Ethylidene-α-D-mannoside* 2 : 3-*Ditoluene*-p-*sulphonate*. Toluene-*p*-sulphonyl chloride (5·7 g.) in pyridine (20 ml.) was mixed with methyl 4 : 6-*O*-ethylidene-α-D-mannoside (2·2 g.) in pyridine (20 ml.) at 0°. The solution was kept at room temperature for 3 days and then poured into ice–water. After several changes of water, with constant stirring, the initial syrup solidified. The dried solid (3·2 g., 60%) was recrystallized from methanol, giving *methyl* 4 : 6-O-*ethylidene-α-D-mannoside* 2 : 3-*ditoluene*-p-*sulphonate*, m. p. 121—122°, $[\alpha]_D^{21}$ −11·6° (*c*, 1·2 in $CHCl_3$) (Found: C, 52·6; H, 5·2; S, 12·4. $C_{23}H_{28}O_{10}S_2$ requires C, 52·2; H, 5·3; S, 12·1%).

Methyl 4 : 6-O-*Ethylidene-α-D-mannoside* 2 : 3-*Dinitrate*.—Fuming nitric acid (4 ml.) in acetic anhydride (10 ml.) was added to an ice-cold suspension of methyl 4 : 6-*O*-ethylidene-α-D-mannoside (4 g.) in acetic anhydride (10 ml.), and after 15 min. at 0° the mixture was stirred into ice–water (200 ml.). After being washed and dried, the resulting solid (92%), m. p. 69—73°, was recrystallized from light petroleum, giving *methyl* 4 : 6-O-*ethylidene-α-D-mannoside* 2 : 3-*dinitrate*, m. p. 73—74°, $[\alpha]_D^{19}$ +20·0° (*c*, 1·3 in $CHCl_3$) (Found: C, 35·0; H, 4·7; N, 8·6. $C_9H_{14}O_{10}N_2$ requires C, 34·8; H, 4·5; N, 9·0%).

Condensation of Propaldehyde with Methyl α-D-Mannoside.—Methyl α-D-mannoside (8 g.), propaldehyde (10 g.), and concentrated hydrochloric acid (1 ml.) were shaken at room temperature for 5 min. After 15 min. more, water was added and the solid was collected. Recrystallization from methanol gave fine needles of *methyl* 2 : 3-4 : 6-*di*-O-*propylidene-α-D-mannoside*, m. p. 92—93°, $[\alpha]_D^{18}$ +5·2° (*c*, 1·0 in $CHCl_3$) (Found: C, 57·4; H, 8·1%; *M*, 277. $C_{19}H_{32}O_6$ requires C, 56·9; H, 8·0%; *M*, 274).

Attempted Nitration of Methyl 2 : 3-4 : 6-*Di*-O-*ethylidene- and -Di*-O-*propylidene-α-D-mannoside*.—The methyl di-*O*-alkylidene-α-D-mannoside (1 g.) in acetic anhydride (2·5 ml.) was mixed with fuming nitric acid (1 ml.) in acetic anhydride (2·5 ml.) at 0°. The solution was allowed to warm to room temperature during 15 min. and then poured into aqueous potassium carbonate. The crude solid which separated was recrystallized and, in each case, was identified as the unchanged di-*O*-alkylidene compound.

Condensation of Benzaldehyde with Methyl α-D-Mannoside.—Methyl α-D-mannoside (20 g.), zinc chloride (15 g.), and benzaldehyde (40 ml.) were shaken at room temperature for 21 hr. The syrup, which separated when the mixture was poured into ice–water, crystallized on trituration with aqueous sodium hydrogen sulphite (10%; 500 ml.). The solid was subsequently washed with aqueous sodium hydrogen carbonate and light petroleum; recrystallization from ethanol–acetone of the residue insoluble in water yielded needles (7 g.) of one of the known isomers of methyl 2 : 3-4 : 6-di-*O*-benzylidene-α-D-mannoside, m. p. 174—178°. A further crop (1·1 g.) of the same compound was obtained from the mother liquors. Robertson (*loc. cit.*) records m. p. 181—182° for this.

The authors thank the Department of Scientific and Industrial Research for the maintenance allowance awarded to J. W. W. M., and Ellis Jones and Co. (Stockport) Ltd. for generous gifts of carob gum.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, November 5th*, 1953.]

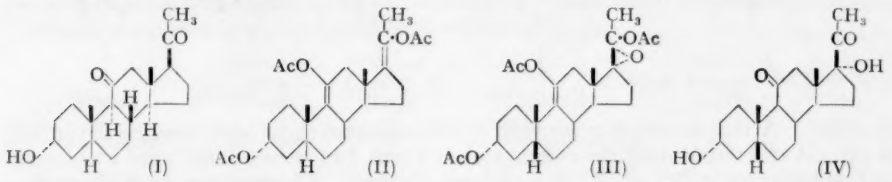
Studies in the Synthesis of Cortisone. Part VII. The Preparation of* 3β : 17α-*Dihydroxy*allo*pregnane*-11 : 20-*dione.*

By D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker.

[Reprint Order No. 4770.]

The 9(11)-double bonds in the dienol acetate (VI) of 3β-acetoxy*allo*pregnane-11 : 20-dione and the monoenol acetate of 3β-acetoxyergostan-11-one (VII) readily react with peracids. Conversion of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) into the $\Delta^{17(20)}$-monoenol acetate (XIV) by treatment with acetic anhydride and perchloric acid in carbon tetrachloride, with subsequent epoxidation and hydrolysis, has given 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (X; R = H) in high yield.

A new reaction sequence for the preparation of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) was described in Part III of this series (*J.*, 1953, 3864). The present paper deals with methods for the introduction of a 17α-hydroxyl group into this compound. A very efficient procedure for this step with compounds of the normal series was described by Kritchevsky, Garmaise, and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 483): they showed that 3α-hydroxypregnane-11 : 20-dione (I), when distilled with toluene-*p*-sulphonic acid and acetic anhydride, afforded a dienol acetate (II), which with perbenzoic acid gave the 17 : 20-monoepoxide (III); 3α : 17α-dihydroxypregnane-11 : 20-dione (IV) was obtained from this by the action of alcoholic sodium hydroxide. The preferential formation of a monoepoxide from (II) was taken as indicative of a 9(11)- rather than an 11(12)-ethylenic linkage. This has been confirmed recently by Hirschmann and Wendler (*ibid.*, 1953, **75**, 2361), who showed that, with compounds analogous to (II), more vigorous epoxidation conditions afford the 9α : 11α-epoxides.



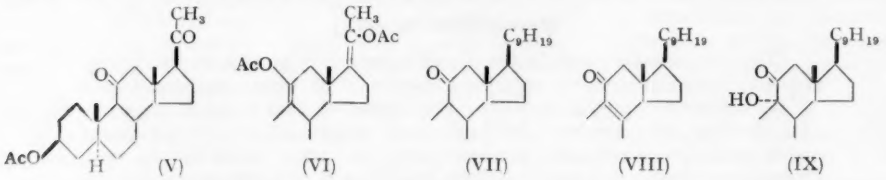
Chemerda, Chamberlin, Wilson, and Tishler (*ibid.*, 1951, **73**, 4052) and Pataki, Rosenkranz, and Djerassi (*ibid.*, 1952, **74**, 5615) applied this method to the *allo*-11 : 20-diketone, but they did not indicate the efficiency of the reactions. In our experience, the yield obtained by this method for the introduction of the 17α-hydroxyl group into 3β-acetoxy*allo*pregnane-11 : 20-dione (V) was only 25—30%, and it seemed that essential differences must exist between the reactions of such diketones in the normal and the *allo*-series.

The dienol acetate (VI), prepared by the method of Marshall, Kritchevsky, Lieberman, and Gallagher (*ibid.*, 1948, **70**, 1837), consumed more than 1 mol. of peracid, the 9(11)- and the 17(20)-bonds both reacting. This might be explained by the smaller steric hindrance of the 9(11)-double bond when rings A and B are *trans*-fused, or the unsaturated linkage might in this instance occupy the 11-position.

To distinguish between these two possibilities similar experiments were carried out on 3β-acetoxyergostan-11-one (VII). The enol acetate of (VII) reacted readily with either perbenzoic or monoperphthalic acid at 20°. The crude product, on hydrolysis, reacetylation, and chromatography, gave principally a hydroxy-compound, which with thionyl chloride in pyridine yielded 3β-acetoxyergost-8(9)-en-11-one (VIII) (cf. Hirschmann and Wendler, *loc. cit.*). It was thus apparent that the product from the hydrolysis of the epoxide was 3β-acetoxy-9α-hydroxyergostan-11-one (IX), that the double bond formed

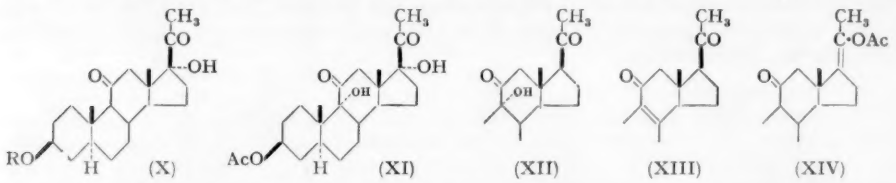
* Part VI, *J.*, 1954, 468.

in the enol esterification occupied the 9(11)-position, and that it was readily attacked by peracids. The 9-hydroxy-group is given the α-configuration by analogy with the structure established for a similar compound in the normal series (Hirschmann and Wendler, *loc. cit.*). The smaller steric hindrance of the 9(11)-ethylenic linkage, in *trans*-A/B-compounds, relative to *cis*-A/B-compounds, revealed by our experiments, is readily understandable on



a confirmational basis (Barton, *Experientia*, 1950, **6**, 316), and is in agreement with observations by Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall (*J. Biol. Chem.*, 1946, **164**, 569) on the inability of 5α-sterols to form 3α : 9α-epoxides.

Chromatography of the reacetylated product from the epoxidation and further processing of the enol acetate derived from (V) gave a diol, in addition to (X; R = Ac). In view of its resistance to acetylation this diol must be ditertiary. For this reason, and from analogy with the above results, it is formulated as 3β-acetoxy-9α : 17α-dihydroxy*allo*pregnane-11 : 20-dione (XI). Consideration of molecular rotations confirms this. The contribution of the 17α-hydroxyl group is −279° {$[M]_D$ of (X) − (V)} and of the 9α-hydroxyl group +77° {$[M]_D$ of (IX) − (VII)}, and these $\Delta[M]_D$'s, when added to the $[M]_D$ of (V) (+330°), give a calculated value for (XI) of +128° compared with an observed value



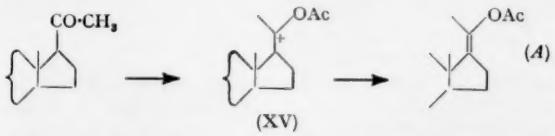
of +183°. Attempts to reduce the yield of this unwanted material by limiting the amount of peracid and terminating the reaction when 1 mol. had been utilised were unsuccessful and, as before, only 25% of (X; R = Ac) was obtained. Chromatography of the mother-liquors yielded an equivalent amount (30%) of 3β-acetoxy-9α-hydroxy*allo*pregnane-11 : 20-dione (XII), which was converted with thionyl chloride and pyridine into 3β-acetoxy*allo*-pregn-8(9)-ene-11 : 20-dione (XIII), whose structure was confirmed by its ultra-violet and infra-red spectra. It was thus apparent that the double bonds in (VI) are both reactive to peracids and that a satisfactory method for the preparation of (X; R = H) could best be achieved by the selective enol esterification of the 20-keto-group.

Saponification values of the enol acetates obtained by the action of acetic anhydride and toluene-*p*-sulphonic acid on (V) and (VII) showed that they contained 2·7 and 1·7 acetyl groups per mole, respectively, whilst the infra-red spectrum of both indicated about 30% of unchanged carbonyl group. So the crude dienol acetate probably contained about 30% of the monoenol acetate (XIV), and the 25% of (X; R = H) formed in this reaction arose from the epoxide of this compound. The optimum yield of (X; R = H) (62%) was obtained by use of 0·1 part (by wt.) of toluene-*p*-sulphonic for 1·5 hours : the crude product then gave a crystalline monoenol acetate in low yield; this, since it is converted into (X; R = H) in 90% yield, must be 3β : 20-diacetoxy*allo*pregn-17(20)-en-11-one (XIV); as the crude enol acetate would be expected to contain 60—70% of (XIV), the low yield is probably due to the isolation of only one of the two possible geometric isomers (cf. Marshall *et al.*, *loc. cit.*). Removal by distillation of the acetic acid formed during the reaction is essential for the enol acetylation of an 11-ketone. When a solution of the ergostane derivative (VII) in acetic anhydride and toluene-*p*-sulphonic acid was heated under reflux,

the starting material was recovered unchanged. Similar treatment of the diketone (V) gave a product in which the 11-ketone was completely untouched, though some disruption of the side-chain had occurred. As no further improvement was achieved with these reagents attention was turned to alternative catalysts.

Polarimetric studies of the effect of small quantities of perchloric acid (cf. Whitman and Schwenk, *J. Amer. Chem. Soc.*, 1946, **68**, 1865; Burton and Praill, *J.*, 1950, **1203**, and references there cited) on a solution of (V) in acetic anhydride at room temperature showed that a rapid reaction took place. The crude product was shown by its saponification value and infra-red spectrum to be essentially the monoenol acetate, and yielded by crystallisation 30% of pure monoenol acetate (XIV). Epoxidation succeeded by hydrolysis then gave a 60% yield of (X; R = H), and this yield was not altered by variation in the amounts of catalyst or the temperature of the reaction.

The mechanism for the enol-acetylation of 20-ketones by acetylium ions may be represented most simply as in (A). Consideration of this mechanism led us to the following simple working hypothesis. The intermediate ion (XV) could undergo two possible



(XV) (A)

reactions: (*a*) elimination of a proton to give the required enol acetate or (*b*) some alternative rearrangement, thus reducing the yield of the required product. On these grounds it seemed possible that, if the life-time of the ion could be reduced, the extent of the side reactions might be limited. Since suitable conditions would be likely to exist in a medium of low dielectric constant, the reaction was examined in a number of such solvents. As would be expected, the reaction was inhibited by ethers, which would have an affinity for the acetylium ion; maximum yields were obtained with solvents of low dielectric constant. The relation between these two factors is shown in the Table.

Solvent	Dielectric const. (approx.)	Yield of (X; R = H) (%)	Solvent	Dielectric const. (approx.)	Yield of (X; R = H) (%)
Acetic anhydride	20·5	67	Benzene	2·28	80
Methylene chloride.....	6·5 (100°)	73	Carbon tetrachloride...	2·2	85
Chloroform	5·0	77	*n*-Hexane	1·87	73
Trichloroethylene	3·4	80			

The result with *n*-hexane might appear at first sight to be anomalous, but since the reaction was carried out in a heterogeneous medium (all the other solvents listed gave a homogeneous medium) it is probable that the solvent was not exerting its full effect. Further investigation showed that the best results could be achieved by using carbon tetrachloride containing 5% of acetic anhydride, which gave a 92% yield of (X; R = H) from (V). Although the use of solvents in this reaction was originally based on the considerations outlined above, we would emphasize that these were only the basis of a working hypothesis and it is also possible that the different yields obtained are due to the influence of the solvent on the further reaction of acetic anhydride with the enol acetate (cf. Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635).

Experimental

$[\alpha]_D$'s were determined on 1% solutions in $CHCl_3$ at room temperature unless otherwise stated: $\lambda_{max.}$ are for solutions in EtOH. A Perkin-Elmer Model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra. The alumina used for chromatography was prepared as described in Part IV (*J.*, 1954, 451). M. p.s were determined on a Kofler block.

Enol Acetylations.—The dienol acetate (VI) and the enol acetate of (VII) were prepared as follows (cf. Marshall *et al.*, *loc. cit.*).

A solution of the ketone (10 g.), acetic anhydride (570 ml.), and toluene-*p*-sulphonic acid

(10 g.) was slowly distilled through a short column for 4 hr., the final volume being 200 ml. Most of the acetic anhydide was removed *in vacuo*, and the residue dissolved in ether, washed with ice cold 5% aqueous sodium hydroxide and water, and dried ($MgSO_4$). On evaporation both enol acetates were obtained as oils. They gave sap. val. of 2·7 and 1·7 respectively, and infra-red spectra indicated about 30% of unchanged keto-group [$\nu_{max.}$ 1706 cm.$^{-1}$ in CS_2 (ketone)].

3β-*Acetoxy*-9α-*hydroxyergostan*-11-*one* (IX).—3β-Acetoxyergostan-11-one (VII) (10 g.) was converted into the enol acetate as above and the resultant gum dissolved in light petroleum (200 ml.; b. p. 40—60°), the solution filtered through acid-washed alumina (20 g.), and the alumina washed with light petroleum (200 ml.); the combined filtrates were evaporated. The resulting gum (9·1 g.) was treated in chloroform (18 ml.) with 2·5N-monoperphthalic acid in ether (50 ml.) at room temperature for 18 hr. After washing of the solution with 5% aqueous sodium hydroxide and water, the solvent was removed and the residue dissolved in hot methanolic 0·8N-potassium hydroxide (60 ml.). After cooling and addition of water, a solid was collected, dried, and acetylated with acetic anhydride (20 ml.) and pyridine (30 ml.) at room temperature to give a solid (6·4 g.). A portion (6 g.) of this was chromatographed on alumina. A fraction was eluted with benzene (800 ml.) and then ether (300 ml.) which on evaporation yielded a solid (3·3 g.), m. p. 170—178°, $[\alpha]_D$ +50°. Recrystallisation from methanol yielded 3β-*acetoxy*-9α-*hydroxyergostan*-11-*one* (IX) as needles (2·1 g.), m. p. 181—182°, $[\alpha]_D$ +49° (Found: C, 76·4; H, 10·5. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%), $\nu_{max.}$ 3500 (hydroxyl), 1733 and 1240 (acetate), and 1694 cm.$^{-1}$ (ketone) in Nujol (C.S. no. 86).*

A portion of this solid (1·0 g.) was dissolved in dry pyridine (5 ml.), and redistilled thionyl chloride (1 ml.) was added. After 1·5 hr. at room temperature the mixture was poured into water and extracted with ether, the ethereal extract washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Removal of the solvent left a solid (0·85 g.) which recrystallised from methanol to give 3β-acetoxyergost-8(9)-en-11-one (VIII) as needles, m. p. 137—139°, $[\alpha]_D$ +121° (Found: C, 79·3; H, 10·5. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%), $\lambda_{max.}$ at 254 mμ (log ε 3·94), $\nu_{max.}$ 1732 and 1240 (acetate), 1660 cm.$^{-1}$ (α : β-unsaturated ketone) in CS_2 (C.S. no. 87) (Laubach *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 1514, give m. p. 138—139°, $[\alpha]_D$ +125°).

Epoxidation of (VI) *and Hydrolysis of the Product.*—(a) *Excess of peracid.* The enol acetate of (V) (9·3 g.), prepared as above, was dissolved in chloroform (20 ml.), 2·2N-monoperphthalic acid in ether (50 ml.) was added, and the mixture kept at room temperature overnight. After being washed with 5% aqueous sodium hydroxide and water, the solution was dried and evaporated. The resulting gum was dissolved in hot methanolic 0·8N-potassium hydroxide (60 ml.), then cooled, water (500 ml.) was added, and the precipitated solid was collected, dried, and acetylated with acetic anhydride (25 ml.) and pyridine (50 ml.) at room temperature. A solid product (6·1 g.) was isolated and a portion (4·0 g.) of this was chromatographed on alumina. A fraction eluted with 50% benzene–ether (1 l.) yielded crude 3β-acetoxy-17α-hydroxy*allo*pregnane-11 : 20-dione (X; R = Ac) (1·95 g.), m. p. 145—155°. Ether eluted another solid (2·9 g.) which, crystallised from benzene, yielded 3β-*acetoxy*-9α : 17α-*dihydroxy*allo*pregnane*-11 : 20-*dione* (XI) as needles (1·35 g.), double m. p. 216—218° and 250—253°, $[\alpha]_D$ +45° in $CHCl_3$, +67° in $COMe_2$ (Found: C, 68·2; H, 8·5. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%), $\nu_{max.}$ 3550 (hydroxyls), 1730, 1248 (acetate), and 1704 and 1710 cm.$^{-1}$ (ketones) in Nujol (C.S. no. 88). This solid (0·4 g.) was dissolved in methanol (10 ml.), and methanolic 0·9N-potassium hydroxide (5 ml.) added. The solution was warmed for a few minutes, then evaporated almost to dryness, water was added and the precipitated 3β : 9α : 17α-*trihydroxy*allo*pregnane*-11 : 20-*dione* was collected; it had m. p. 305—308°, $[\alpha]_D$ +88° (*c*, 1·0 in dioxan) (Found: C, 69·2; H, 8·9. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·8%).

(b) 1 *Mol. of peracid.* The dienol acetate (VI), prepared as described above, was oxidised overnight in ether with 1 mol. of 0·3N-monoperphthalic acid. Titration showed that approx. 90% of the available oxygen had been used. The epoxide was isolated by the addition of more ether, washing of the organic layer with three portions of ice-cold sodium hydrogen carbonate solution and then with water, drying ($MgSO_4$), and removal of the solvent *in vacuo*. The gummy epoxide was hydrolysed by dissolving it in warm dry ethanol (630 ml.), adding 10 ml. of tetrahydrofuran, followed by aqueous 0·6N-sodium hydroxide (630 ml.). The solution was kept at room temperature for 1 hr., then some solvent was removed *in vacuo* and the solid which was precipitated was removed and washed with a little water and acetone. The solid was then warmed with a little chloroform and the mixture cooled and filtered. The residual solid was

* Spectra thus marked have been deposited with the Society. Photocopies, price 3*s*. 0*d*. per copy per spectrum, may be obtained on application to the General Secretary, quoting the C.S. no.

recrystallised from methanol, to give 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (X; R = H) (8 g.), double m. p. 267—271° and 286—289°, $[\alpha]_D$ +65° in dioxan (Found : C, 72·6; H, 9·4. Calc. for $C_{21}H_{32}O_4$: C, 72·4; H, 9·2%), $\nu_{max.}$ 3400, 3330 (hydroxyl), 1692 and 1702 cm.$^{-1}$ (ketone) in Nujol (C.S. no. 89). The mother-liquors from the hydrolysis and the washings were combined, more water was added, and the organic material was extracted with chloroform. Removal of the chloroform gave a gum which was acetylated with acetic anhydride and pyridine at room temperature to yield a solid (17·7 g.) which was chromatographed on alumina. A fraction was eluted with light petroleum (b. p. 40—60°)–ether (1 : 1) which on evaporation gave a solid (7·6 g.) which crystallised from acetone–petrol to give 3β-*acetoxy*-9α-*hydroxy*allo*pregnane*-11 : 20-*dione* (XII) (5·3 g.), m. p. 209—211°, $[\alpha]_D$ +105° in $COMe_2$ (Found : C, 71·2; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·8%). A second fraction (3·1 g.), eluted with light petroleum and ether containing 1% of methanol, and crystallised from benzene, gave 3β-acetoxy-9α : 17α-dihydroxy-*allo*pregnane-11 : 20-dione (XI), double m. p. 216—218° and 250—253°, $[\alpha]_D$ +45°.

Dehydration of 3β-*Acetoxy*-9α-*hydroxy*allo*pregnane*-11 : 20-*dione* (XII).—The hydroxy-compound (XII) (2 g.) in dry pyridine (10 ml.) was kept at room temperature with thionyl chloride (2 ml.) for 1 hr., then poured into a large volume of water. The organic material was extracted into ether, the extract washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the resulting gum on alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave a solid (1·13 g.) which after two crystallisations from aqueous methanol gave 3β-*acetoxy*-allo*pregn*-8(9)-*ene*-11 : 20-*dione* (XIII) (0·59 g.), m. p. 129—131°, $[\alpha]_D$ +194° in $COMe_2$ (Found : C, 73·8; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·15; H, 8·7%), $\lambda_{max.}$ 254 mμ (log ε 3·95), $\nu_{max.}$ 1734 and 1240 (acetate), 1712 (ketone), 1668 cm.$^{-1}$ (α : β-unsaturated ketone) in CS_2 (C.S. no. 90)

Isolation of 3β : 20-*Diacetoxy*allo*pregn*-17(20)-*en*-11-*one* (XIV).—(a) *With toluene*-p-*sulphonic acid.* A solution of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) (5 g.), toluene-*p*-sulphonic acid (0·5 g.), and acetic anhydride (100 ml.) was slowly distilled for 1·5 hr., further acetic anhydride being added to keep the volume constant. The solution was cooled, ether added, and the solution washed with ice-cold 5% sodium hydroxide solution and water, and dried ($MgSO_4$), and the solvent evaporated. The residual gum dissolved in light petroleum (b. p. 40—60°) was filtered through acid-washed alumina, and the solution concentrated and set aside at 0°. The resulting solid was crystallised twice more from the same solvent, to give the *monoenol acetate* (XIV; 1 g.), m. p. 152—154°, $[\alpha]_D$ +7° (Found : C, 72·3; H, 8·6%; OAc, 1·02 equiv. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%), $\nu_{max.}$ 1756 and 1215 (enol acetate), 1735, 1242 (acetate) and 1708 cm.$^{-1}$ (ketone) in CS_2 (C.S. no. 91). This was converted into (X; R = H) in 92% yield by the method described below.

(b) *With perchloric acid.* 3β-Acetoxy*allo*pregnane-11 : 20-dione (V) (10 g.) in carbon tetrachloride (95 ml.) was treated at room temperature with 50% aqueous perchloric acid (0·2 ml.) in acetic anhydride (5 ml.). After 1·5 hr. at room temperature, the solution was washed with ice-cold 5% sodium hydroxide solution and water, then dried ($MgSO_4$), and the solvent removed *in vacuo*. The semicrystalline residue was taken up in light petroleum (b. p. 40—60°). A solid gradually separated, which, twice recrystallised from light petroleum, yielded the enol acetate (XIV) (3·2 g.) (Sap. val., 0·98)

3β : 17α-*Dihydroxy*allo*pregnane*-11 : 20-*dione* (X; R = H).—3β-Acetoxy*allo*pregnane-11 : 20-dione (V) (10 g.) was converted into its enol acetate as described in the previous experiment. The crude residue was taken up in chloroform (20 ml.) and a solution of monoperphthalic acid in ether (2N; 55 ml.) added. After 3 hr. at room temperature, the product was isolated in the usual manner. The gummy material remaining after removal of the solvent was treated with hot methanolic 0·8N-potassium hydroxide (80 ml.) with rapid swirling and further heating. The solution became clear and almost immediately crystalline material started to separate. The solution was cooled rapidly to room temperature, water added, and the solid filtered off, washed with water, and dried *in vacuo* (P_2O_5) at room temperature, to give pure (X; R = H) (8·4 g., 92%), double m. p. 267—271° and 286—289°, $[\alpha]_D$ +65° in dioxan (*c*, 0·5), $\nu_{max.}$ 3400, 3330 (hydroxyls), 1692 and 1702 cm.$^{-1}$ (ketones) in Nujol.

Thanks are offered to Mr. P. J. Palmer, Mr. P. J. Halcox, and Mr. S. G. Brooks for assistance with the experimental work.

Birkbeck College, London, W.C.1.
Glaxo Laboratories Ltd., Greenford, Middlesex. [*Received, November 6th*, 1953.]

Wood Saponins. Part I. A Preliminary Investigation of the Saponins from Morabukea [Mora gonggrijpii (*Kleinh.*) *Sandwith*].

By R. A. Laidlaw.

[Reprint Order No. 4714.]

Acid hydrolysis of morabukea saponin gave oleanolic acid (30%) and a mixture of sugars (70%) containing D-galactose (8·4%), D-glucose (56·1%), and D-xylose (35·5%). Acetylation of the saponin, methylation, and hydrolysis yielded methyl oleanolate and a mixture of methylated sugars containing tetra-*O*-methyl-D-glucopyranose (62 parts), tetra-*O*-methyl-D-galactopyranose (3 parts), 2 : 4 : 6-tri- (12 parts) and 3 : 4-di-*O*-methyl-D-glucose (2 parts), tri-*O*-methyl-D-galactoses (9 parts), 2 : 3- (4 parts) and 2 : 4-di-*O*-methyl- (2 parts), and 2- (20 parts) and 3-*O*-methyl-D-xylose (20 parts), along with traces of other methylated derivatives and of xylose. Since no single structural formula could account for such a complex mixture, the material must comprise several distinct components.

The crude saponin isolated from morabukea (Farmer and Campbell, *Nature*, 1950, **165**, 237) had a small ash content and contained traces of free galactose and arabinose in admixture. Acid hydrolysis liberated oleanolic acid, D-galactose, D-glucose, and D-xylose.

Our saponin was purified by acetylation and deacetylation. Hydrolysis of the product gave oleanolic acid (30%) and quantitative examination on the paper chromatogram (Duff and Eastwood, *Nature*, 1950, **165**, 848) of the mixture of sugars produced showed galactose 8·4%, glucose 56·1%, and xylose 35·5%. These results, taken in conjunction with hypoiodite estimations of the total reducing sugars liberated, indicated the oleanolic acid : galactose : glucose : xylose ratio to be approximately 1 : 0·4 : 3 : 2.

Methylation of the acetate with methyl sulphate and sodium hydroxide followed by several treatments with methyl iodide and silver oxide gave a methylated material (OMe, 29·2%, not raised by further methylation). Hydrolysis gave methyl oleanolate and a mixture of sugars which by partition on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) gave the following substantially pure materials: crystalline 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose (51·7%; this and the following percentages are based on the weight of material recovered from the column), 2 : 4 : 6-tri-*O*-methyl-D-glucose (9·2%), crystalline 2-*O*-methyl- (6·4%) and 2 : 3- (2·2%) and crystalline 2 : 4-di-*O*-methyl-β-D-xylose (1·4%), 3 : 4-di-*O*-methyl-D-glucose (1·4%), and a small amount of 3-*O*-methyl-D-xylose. The trimethylglucose was identified by its R_G value, methoxyl content, specific rotation, and demethylation to glucose, by its failure to yield a methyl furanoside with cold methanolic hydrogen chloride or formaldehyde with periodate, and by the negative Weerman test given by the derived amide. The 2 : 3-di-*O*-methyl-D-xylose and 3 : 4-di-*O*-methyl-D-glucose were identified by their R_G values, methoxyl contents, and failure to yield formaldehyde with periodate.

In addition the following less pure fractions were obtained:

(*a*) A mixture (22·8%) of 2- and 3-*O*-methyl-D-xylose, from which the above-mentioned quantities of the pure monoethers were isolated. The whole mixture gave only xylose on hydrolysis. Ionophoresis of the non-crystalline portion at pH 10 (cf. Foster, *J.*, 1953, 982) indicated the presence of the two ethers in a proportion of *ca.* 1 : 2; the derived lactone mixture had $[\alpha]_D^{18}$ +84° ⟶ 51° (in 500 hr. in H_2O) which, from the known rotations of the pure lactones (Percival and Willox, *J.*, 1949, 1608; Laidlaw and Percival, *J.*, 1950, 528) and on the assumption of equal ease of lactonisation, again indicated a 1 : 2 ratio. The lactones were converted into the amides which with alkaline hypochlorite and semicarbazide, yielded 20% of hydrazodicarbonamide; since 3-*O*-methyl-D-xylonamide gives a *ca.* 33% yield under similar conditions (Laidlaw and Percival, *J.*, 1949, 1600), the content of this amide can be calculated to be about 61%, which again gives the 1 : 2 ratio. These results, with the yields of crystalline materials isolated, indicate that the mixture (*a*) contained about equal parts of the two ethers.

(*b*) A mixture (7·2%) on demethylation (Hough, Jones, and Wadman, *J.*, 1950, 1702)

gave galactose and a small amount of glucose. The galactose derivatives were all trimethyl ethers, as shown by analysis of the aniline derivatives; the 2 : 3 : 6-trimethyl ether was absent (failure to give a methyl furanoside under the conditions mentioned above), as was the 3 : 4 : 6-trimethyl ether (failure of the derived amides to give a Weerman test), and the derived lactones were of δ-type, so that the fraction contained mainly 2 : 3 : 4- and 2 : 4 : 6-tri-*O*-methyl-D-galactose; the proportions of these cannot be calculated—the formaldehyde–dimedone derivative (30%) obtained by use of periodate, etc., was impure. The glucose component, was, on the basis of its R_G value, 2 : 3-di-*O*-methyl-D-glucose, and this accords with the low methoxyl content of the total fraction.

(*c*) A tetramethyl ether fraction (2·6%) also gave galactose with a little glucose on demethylation; identification of a crystalline aniline derivative showed the main constituent to be 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, and the R_G value indicated that the contaminant was 2 : 3 : 4-tri-*O*-methylglucose.

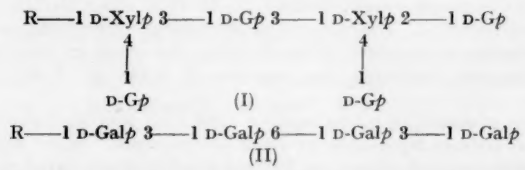
(*d*) A small fraction (0·5%) had the R_G value of 2 : 3 : 6-tri-*O*-methylglucose but was not further investigated.

Traces of free xylose were also identified among the hydrolysis products. This material, however, almost certainly arose from the demethylation known to occur when mono-*O*-methylxyloses are heated with acids (cf. Laidlaw and Percival, *J.*, 1949, 1600), while the dimethylxyloses may be cleavage products of degraded methylated saponin. A trial hydrolysis carried out with tetra-*O*-methyl-D-glucopyranose showed that no appreciable demethylation was effected under the conditions used in the hydrolysis of the methylated saponin and, therefore, the partially methylated glucose derivatives found could not have arisen by destruction of the fully methylated material. Oxidation of the free saponin with sodium periodate gave a product which on hydrolysis yielded xylose along with small amounts of glucose. Since glucose residues linked through $C_{(1)}$ or through $C_{(1)}$, $C_{(2)}$, and $C_{(6)}$ would be split by the reagent, it follows that the glucose found must have been derived from residues linked through $C_{(1)}$ and $C_{(3)}$; the origin of the small amounts of methylated glucoses other than the 2 : 4 : 6-derivative which have been found is obscure, though some of these are probably artifacts arising by incomplete methylation.

While it is evident that the starting product is a mixture, no fractionation of the components has been achieved so far.

Partial hydrolysis of the saponin yielded a substance containing oleanolic acid and xylose only, indicating that, in one component of the mixture at least, the sapogenin is linked directly to xylose. Attempts to isolate a disaccharide containing xylose residues only from the saponin degradation products were unsuccessful. The alkali-stability of the saponin and its non-reducing properties indicate that the terminal reducing groups of the oligosaccharide chains are joined to the sapogenin through the hydroxyl group of the latter.

In view of the heterogeneous nature of the material, no single structural formula can be ascribed to the product; a structure such as (I), one of several possible variants, would explain many of the properties of the saponin.



Where R = oleanolic acid, joined through the hydroxyl group. For conventional symbols, see *J.*, 1952, 5121.

The role of the galactose in the saponin molecule cannot be decided as yet. While it may form part of a " mixed " saponin, it is also possible that it may be derived from a compound containing only oleanolic acid and galactose residues, such as (II).

The amounts of periodate reduced and formic acid liberated on periodate oxidation of the saponin agree with the methylation evidence that the molecule is highly branched.

Experimental

Evaporations were conducted under diminished pressure. Temperatures recorded are bath-temperatures. Fractions from the cellulose column were evaporated to dryness; solutions of the residues in water were digested with charcoal and filtered hot, then evaporated to dryness; these residues were exhaustively extracted with boiling acetone, and the extracts were evaporated to dryness.

The saponin, prepared from the heartwood of morabukea [*Mora gonggrijpii* (Kleinh.) Sandwith; Farmer and Campbell, *loc. cit.*], was kindly supplied by Dr. R. H. Farmer.

The product gave 3·0% of ash (as sulphate; magnesium, potassium, and sodium were identified). The aqueous solution did not reduce boiling Fehling's solution.

The sapogenin has been identified as oleanolic acid (R. H. Farmer, personal communication). Hydrolysis of the saponin with ethanolic hydrogen chloride (Marker, Wagner, Ulshafer, Wittbecker, Goldsmith, and Ruop, *J. Amer. Chem. Soc.*, 1947, **69**, 2167) yielded the crystalline acid which, after purification *via* the acetate, m. p. 266—267°, $[\alpha]_D^{20}$ +73·5° (*c*, 2·2 in $CHCl_3$), had m. p. 299—301°, $[\alpha]_D^{20}$ +74° (*c*, 2·0 in $CHCl_3$). Mixed m. p. determinations with authentic specimens showed no depression.

Acetylation.—The saponin (20 g.) was dissolved in pyridine (200 c.c.), acetic anhydride (140 c.c.) was added with stirring, and the whole was left overnight at room temperature. The acetate was precipitated with water, filtered off, and washed free from pyridine; its solution in chloroform was dried (Na_2SO_4), filtered, and evaporated to small volume. The purified acetate was precipitated by the addition of light petroleum (b. p. 60—80°; 2 l.). Attempts to fractionate the product by stepwise precipitation or dissolution were ineffective. The acetate (23 g.) had $[\alpha]_D^{17}$ −13° (*c*, 2·03 in $CHCl_3$) and OAc 35·9%.

Deacetylation.—The acetate (7 g.) was treated with 0·4N-sodium hydroxide (500 c.c.) at room temperature for 24 hr. The resulting solution was de-ionised with resins ("Zeocarb 215" and "Deacidite E"), and evaporated to small volume, decyl alcohol being used to minimise frothing. Ethanol (150 c.c.) was added and the mixture evaporated to dryness. The residue was redissolved in ethanol, the solution filtered and evaporated to small volume, and excess of acetone added. The precipitated saponin was removed at the centrifuge, washed with acetone, and dried in a vacuum-desiccator ($CaCl_2$); it had $[\alpha]_D^{19}$ −4° (*c*, 2·1 in H_2O) (yield, 3 g.).

Hydrolysis with Sulphuric Acid.—The purified saponin (2 g.) was heated with N-sulphuric acid (50 c.c.) at 100°. $[\alpha]_D^{19}$ were +9° (1 hr.), +22° (6 hr., constant). After neutralisation and filtration the filtrate was evaporated to a syrup. Quantitative chromatography (*loc. cit.*) indicated the presence in the syrup of only galactose 8·4%, glucose 56·1%, and xylose 35·5%.

The syrup partly crystallised. Trituration with glacial acetic acid and recrystallisation of the residue from ethanol yielded α-D-glucopyranose, m. p. and mixed m. p. 140—142°, $[\alpha]_D^{18}$ +91° (5 min.), +77° (1 hr.), +52° (24 hr.). Evaporation of the acetic acid washings gave a syrup in which D-xylose was identified as the di-*O*-benzylidene dimethyl acetal (Breddy and Jones, *J.*, 1945, 738), m. p. and mixed m. p. 207—209°, $[\alpha]_D^{19}$ −7° (*c*, 2·1 in $CHCl_3$). Treatment of a portion of the syrup with methylphenylhydrazine gave D-galactose methylphenylhydrazone, m. p. and mixed m. p. 180° (cf. Hirst, Jones, and Woods, *J.*, 1947, 1048).

The purified saponin (0·7767 g.) was hydrolysed as above. The solution was cooled and filtered through a tared alundum crucible. The residue was washed thoroughly with water and dried at 105° to constant weight (0·2594 g., 33·4%). The filtrate and washings were combined and made up to 200 c.c. The reducing sugars present were estimated on aliquot portions by oxidation with alkaline hypoiodite. Assuming that the sugar mixture has the composition found above, the analysis indicated the presence of 0·448 g. of anhydro-sugars. Total recovery = *ca.* 90%.

Methylation.—The acetate (14 g.) in acetone (200 c.c.) was methylated four times with methyl sulphate and sodium hydroxide at room temperature. After each methylation the acetone was removed in a partial vacuum, at 75°, and the solid methylated material was removed by filtration and washed with hot water. After the fourth methylation the product was dissolved in chloroform, and the solution was dried (Na_2SO_4) and evaporated to a syrup (11·5 g.; OMe, 27·6%) which was methylated five times with the Purdie reagents; the methylated saponin was obtained as a brittle glass {10·5 g.; $[\alpha]_D^{19}$ −9° (*c*, 3·02 in $CHCl_3$); OMe, 29·2%}. The properties of this product were unchanged by further methylation, even by the sodium–methyl iodide method (Pacsu and Trister, *J. Amer. Chem. Soc.*, 1939, **61**, 2442).

Methanolysis, Hydrolysis, and Fractionation.—The methylated saponin (7·3 g.) was heated with methanolic hydrogen chloride (3%; 300 c.c.) under reflux for 5 hr., neutralised with silver

carbonate, and filtered. The solution gradually deposited crystalline methyl oleanolate (m. p. 198° after recrystallisation from methanol). The mother-liquors were evaporated to dryness and the residue heated with N-sulphuric acid (200 c.c.) for 11 hr. The solution was filtered free from methyl oleanolate (2 g.) (Found: OMe, 5·8. Calc. for $C_{31}H_{50}O_3$: OMe, 6·6%), and the filtrate was neutralised with barium carbonate. Filtration, evaporation, and extraction of the residue with boiling acetone gave mixed methylated sugars (4·2 g.) which were heated with nitric acid (2%; 100 c.c.) at 100° for 2 hr. (rotation constant). The product (3·80 g.) was recovered in the usual manner and fractionated on a column of cellulose (25″ × 1·5″) (Hough, Jones, and Wadman, *loc. cit.*) with 2 : 3 butanol–light petroleum (b. p. 100—120°), saturated with water, as eluant. This gave fractions (1) 1·599 g., (2) 0·082 g., (3) 0·420 g., (4) 0·221 g., (5) 0·069 g., and (6) 0·705 g. (recovery, 3·096 g., 81·5%). Traces of xylose were also found.

Fractions (3) and (5) were mixtures. Fraction (3) was refractionated on cellulose as above, to yield (3*a*) 0·013 g., (3*b*) 0·247 g., (3*c*) 0·007 g., (3*d*) 0·060 g., and (3*e*) 0·038 g. Fraction (5) was fractionated on Whatman's 3 MM paper with butanol–ethanol–water (4 : 1 : 5) as solvent, to give (5*a*) 0·029 g. and (5*b*) 0·016 g.; the latter was combined with fraction (6).

Fraction 1. This had R_G 1·00 and crystallised completely, to give 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, which, on recrystallisation from ether–light petroleum (b. p. 40—60°), had m. p. and mixed m. p. 94°, $[\alpha]_D^{18}$ +97° (2 min.), +93° (20 min.), +89° (50 min.), +81° (24 hr., constant) (*c*, 1·95 in H_2O) (Found: C, 50·8; H, 8·5; OMe, 53·4. Calc. for $C_{10}H_{20}O_6$: C, 50·8; H, 8·5; OMe, 52·5%).

Fraction (2). This travelled at the same rate on the chromatogram as tetra-*O*-methyl-galactopyranose and had OMe 49·3%. Treatment of the syrup with aniline in ethanol gave tetra-*O*-methyl-*N*-phenyl-D-galactopyranosylamine, m. p. and mixed m. p. 194°, $[\alpha]_D^{18}$ −77° (*c*, 0·21 in acetone). A small portion of the aniline derivative failed to crystallise. This syrupy material was decomposed with sulphuric acid and the liberated free sugars were demethylated with hydrobromic acid (46—48%) (Hough, Jones, and Wadman, *loc. cit.*). Chromatography, with butanol–pyridine–water–benzene (5 : 3 : 3 : 1) as solvent, indicated the presence of both glucose and galactose.

Fraction (3*a*). This had the same R_G value as 2 : 3 : 6-tri-*O*-methylglucopyranose, and was not further investigated.

Fraction (3*b*). This had the same R_G value as 2 : 4 : 6-tri-*O*-methylglucopyranose (Found: OMe, 40·8. Calc. for $C_9H_{18}O_6$: OMe, 41·8%) and $[\alpha]_D^{18}$ +84° (*c*, 1·25 in H_2O). Fraction (3*b*) (0·2075 g.) was dissolved in methanolic hydrogen chloride (1%; 11 c.c.); $[\alpha]_D^{17}$ (+87·5°) was unchanged after 24 hr. at room temperature. The solution was neutralised (silver carbonate), filtered, and evaporated to dryness, and the residue heated with N-sulphuric acid, to give a reducing syrup. This (10 mg.), on demethylation with hydrobromic acid, gave glucose only, identified on the paper chromatogram.

Oxidation of fraction (3*b*) with periodate (Reeves, *loc. cit.*) gave no formaldehyde. Bromine oxidation yielded a syrupy lactone which was converted into the amide (negative Weerman test).

Fraction (3*c*). This was a mixture of (3*b*) and (3*d*).

Fraction (3*d*). This had the same R_G value as 2 : 3-di-*O*-methylxylose (Found: OMe, 32·0. Calc. for $C_7H_{14}O_5$: OMe, 34·8%) and had $[\alpha]_D^{19}$ +21° (*c*, 0·5 in H_2O). Demethylation gave xylose only, and periodate oxidation gave formaldehyde, identified as the dimedone compound, m. p. and mixed m. p. 186—188°.

Fraction (3*e*). This travelled on the chromatogram at the same rate as 2 : 4-di-*O*-methyl-xylose, and crystallised completely, to give 2 : 4-di-*O*-methyl-β-D-xylose, m. p. and mixed m. p. 108° (Found: C, 46·8; H, 7·75; OMe, 33·0. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; OMe, 34·8%).

Fraction (4). This did not crystallise (Found: OMe, 37·5. Calc. for $C_9H_{18}O_6$: OMe, 41·8%) and had $[\alpha]_D^{18}$ +121° (*c*, 1·5 in H_2O). Demethylation gave galactose along with small amounts of glucose.

Syrup (4) (*ca.* 120 mg.) was heated with aniline in ethanol, and on removal of the solvent by gradual evaporation in a vacuum-desiccator the following crops of crystals were obtained: (i) 7·4 mg., m. p. 101° with previous softening (Found: N, 5·35; OMe, 27·7%), (ii) 15 mg., m. p. 119°, (iii) 50 mg., m. p. 120°, unchanged on admixture with crop (ii) (Found: C, 59·7; H, 7·5; N, 4·9; OMe, 29·8. Calc. for $C_{14}H_{21}O_5N$: C, 57·6; H, 7·5; N, 4·95; OMe, 21·9. Calc. for $C_{15}H_{23}O_5N$: C, 60·6; H, 7·8; N, 4·7; OMe, 31·3%).

Treatment of fraction (4) with 1% methanolic hydrogen chloride at room temperature caused a change of $[\alpha]_D^{18}$ +72° to +120° (24 hr.). Oxidation with bromine water yielded the lactone which was distilled at 150°/0·10 mm. The syrupy product had $[\alpha]_D^{18}$ +125° (20 min.),

+88° (1½ hr.), +25° (4½ hr.), +3° (24 hr., constant) (*c*, 1·5 in H_2O). Oxidation of the lactone (16·9 mg.) with periodate gave formaldehyde, identified as the dimedone compound (8·0 mg., m. p. *ca.* 160°). The lactone was recovered from the polarimetric solution by evaporation and was redistilled as before. The product crystallised immediately, but in quantity too small for further investigation. The lactone was converted into the amide by methanolic ammonia and the partly crystalline product gave a negative Weerman test.

Fraction (5*a*). This travelled on the chromatogram at the same rate as 3 : 4-di-*O*-methylglucose (Found: OMe, 26·1. Calc. for $C_8H_{16}O_6$: OMe, 29·8%). Demethylation yielded glucose, along with traces of galactose. Oxidation with periodate gave formaldehyde in small yield (dimedone compound, m. p. and mixed m. p. 186°). The fraction travelled at a slightly different rate from 2 : 4-di-*O*-methylglucose on the chromatogram and was much slower than 2 : 3-di-*O*-methylglucose.

Fraction (6). The syrup (OMe, 17·5%) partly crystallised during several days. The crystals were separated on a tile and triturated with light petroleum (b. p. 40—60°)–acetone (3 : 1). The very small quantity of hygroscopic crystalline material had m. p. 95—97°, unchanged on admixture with 3-*O*-methyl-D-xylose. The tile was exhaustively extracted with boiling acetone and the extracts were combined with the light petroleum mother-liquors and evaporated to dryness. The residue was dissolved in ethanol, and the solution was evaporated slowly to small volume in a vacuum-desiccator. The crystals which separated were removed by filtration and washed with ethanol–light petroleum (b. p. 60—80°) (1 : 3). The yield was 0·15 g., the m. p. 137—138°, unchanged on admixture with an authentic specimen of 2-*O*-methyl-D-xylose, and $[\alpha]_D^{19}$ −21° (3 min.), +1° (11 min.), +27° (30 min.), +34° (2 hr., constant value) (*c*, 0·73 in H_2O) (Found: C, 44·2; H, 7·3; OMe, 19·5. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·4; OMe, 18·9%). Evaporation of the combined filtrates and washings gave a syrup (OMe, 17·0%) which was examined by paper ionophoresis (cf. Foster, *loc. cit.*) on Whatman's No. 1 filter sheet at 400 v in borate buffer (pH 9·97). Both 2- and 3-*O*-methylxylose were detected (the complexes travelled 6·8 and 13·6 cm. respectively in 3¾ hr.).

The syrup did not crystallise further. Oxidation of this product (0·3 g.) with bromine, and distillation of the mixture of lactones at 145—155°/0·01 mm., yielded a syrup (0·19 g.) having $[\alpha]_D^{19}$ +84° (20 min.), +80° (22 hr.), +65° (166 hr.), +57° (333 hr.), +51° (500 hr., constant) (*c*, 1·39 in H_2O) (10·8 mg. required 6·03 c.c. of 0·01135N-sodium hydroxide for neutralisation. Calc. for $C_6H_{10}O_5$: 5·87 c.c.).

Treatment of the lactones with methanolic ammonia gave the corresponding amides. The syrupy mixture (60 mg.) with alkaline hypochlorite and semicarbazide hydrochloride (Weerman, *Rec. Trav. chim.*, 1917, **37**, 16) yielded hydrazodicarbonamide (7·6 mg., 20%), m. p. and mixed m. p. 256°.

Periodate Oxidation Experiments.—These were carried out on portions of the saponin purified by acetylation and deacetylation.

Formic acid. The saponin was oxidised with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427), and the formic acid liberated was determined with 0·01N-sodium hydroxide, *viz.*: 0·728 (2 days), 0·914 (4 days), 1·14 (6 days, constant) × 10^{-3} mole of formic acid per g. of saponin.

Periodate uptake. To the saponin (*ca.* 0·2 g.) in water (35 c.c.) sodium metaperiodate (15 c.c.; 0·3M) was added. The periodate content, determined in portions (5 c.c.) by the arsenite method, was 5·14 (4 days), 5·79 (6 days, constant) × 10^{-3} mole of periodate consumed per g. of saponin.

Formaldehyde production. The saponin (0·5 g.) was dissolved in 0·3M-sodium metaperiodate (15 c.c.) and left at room temperature for 76 hr. No formaldehyde was produced.

Identification of free sugars among the hydrolysis-products of periodate-oxidised saponin. The saponin (0·5 g.) in water (30 c.c.) was treated with 0·3M-sodium metaperiodate (30 c.c.) at room temperature for 5 days. Iodate and periodate were destroyed by the addition of sodium arsenite (30 c.c.; 1·2M). Ions were removed by columns of resins, and the solution was evaporated to dryness. The residue was hydrolysed by sulphuric acid (2N; 20 c.c.) at 100° for 5 hr. Neutralisation, filtration, and evaporation left a syrup which on the chromatogram was shown to contain xylose along with smaller amounts of glucose. Traces of galactose appeared to be present also.

Oleanolic acid. Recrystallised oleanolic acid (0·5 g.), suspended in water and oxidised as above, did not take up periodate.

Hydrolysis of the Saponin with Acetic Acid.—The crude saponin (2 g.) was heated at 100° with acetic acid (20%; 100 c.c.) for 4½ hr. Some solid material separated and was removed

by filtration. Complete hydrolysis of this product with 4N-sulphuric acid and examination of the products on the paper chromatogram indicated the presence of xylose along with very small amounts of other sugars.

The filtrate was neutralised and evaporated to dryness. Examination on the chromatogram showed the presence of glucose, a little galactose, and some oligosaccharides. Only very small amounts of xylose were detected.

Acetolysis of the Saponin.—The saponin (10 g.) was heated in boiling acetic anhydride (50 c.c.) containing zinc chloride (2 g.) under reflux for 1 hr., then poured into ice-water; the acetate was separated by filtration and washed with water, then deacetylated with sodium methoxide in chloroform (Zemplen and Pacsu, *Ber.*, 1929, **62**, 1613). Examination of the product on the chromatogram showed the presence of a range of oligosaccharides, each of which gave mixtures of free sugars on hydrolysis.

Other Fractionations.—Effective fractionation could not be obtained by fractionation on a charcoal column (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677); the product eluted in low yield by 50% ethanol had the same properties as the starting material and gave similar acetylated and methylated derivatives. Attempts to separate the components of the saponin mixture by fractional dissolution in ethanol were unsuccessful. In an effort to split off methyl oleanolate without disrupting the methylated oligosaccharide chain, several methods of hydrolysis were tried: in both aqueous and non-aqueous solvents the strength of acid necessary to cleave the sapogenin linkage also caused considerable breakdown of the oligosaccharide residue.

The author thanks Dr. R. H. Farmer for a supply of saponin and for helpful comment, and Professor E. L. Hirst, F.R.S., for his interest and for use of the ionophoresis apparatus. Thanks are also expressed to Mr. R. Mahomed for performing the ionophoresis experiment and to Drs. E. E. Percival and D. J. Bell for specimens of methylated sugars. This work forms part of the current research programme of the Forest Products Research Board, and is published by permission of the Department of Scientific and Industrial Research.

Section of Chemistry, Forest Products Research Laboratory,
Princes Risborough, Aylesbury, Bucks. [*Received, October 10th*, 1953.]

NOTES.

Observations on the Synthesis of [8-^{13}C]*Adenine.*

By Maxwell Gordon.

[Reprint Order No. 4657.]

In the synthesis of [8-^{14}C]adenine by cyclization of 4 : 6-diamino-5-formamidopyrimidine in formamide, Cavalieri and Brown (*J. Amer. Chem. Soc.*, 1949, **71**, 2246) originally noted a 75% exchange of the labelled formyl group with the unlabelled formic acid from the formamide. Clark and Kalckar (*J.*, 1950, 1029) reported that this exchange could be reduced to about 20% by the use of 4-formylmorpholine as the cyclizing solvent. Abrams and Clark (*J. Amer. Chem. Soc.*, 1951, **73**, 4609) were unable to repeat Clark and Kalckar's work, and postulated a diformamidopyrimidine which could cyclize in either direction to give a theoretical maximum of 50% isotope incorporation.

We have made labelled adenine by Clark and Kalckar's procedure using ^{13}C, thus avoiding any counting error such as that postulated by Abrams and Clark. We have

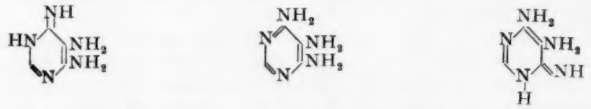
Expt. no.	H·CO_2H (atom % excess of ^{13}C)	Adenine (atom % excess of ^{13}C)	Wt. yield * (%, based on formate)	Isotope yield (%)
1	42·5	6·67	36·1	78·5
2	42·5	6·45	28·4	76
3	42·5	6·79	22·0	80

* Syntheses on a 1 mmole scale.

succeeded in carrying out repeated syntheses in which the incorporation of isotope into the adenine was in excess of 75% (cf. Table). Thus our results support those of Clark and Kalckar. Data from chemical reactivity and spectra show that the 4- and the 6-amino-group have some imine character and are less reactive than the 5-amino-group. Hence all these formamido-groups would not be expected to be equally reactive, as would

be required by Abrams and Clark's postulate. Indeed, to our knowledge, no diformyl-4 : 5 : 6-triaminopyrimidine has been isolated.

Some of the potential tautomeric forms of 4 : 5 : 6-triaminopyrimidine are shown below to illustrate the partial imine character of the 4- and the 6-amino-group :



Abrams and Clark have speculated that the discrepancies between their own results and those of Clark and Kalckar were due to (1) the use of the formamido-compound as the sulphate rather than as the hydrochloride, and (2) the fact that direct plating rather than combustion of ^{14}C-samples to barium carbonate might have been used to prepare ^{14}C-compounds for counting. Regarding the first possibility we have no information. The second speculation is improbable for two reasons. First, our work was done with ^{13}C with which this counting problem does not arise, and, secondly, results on determination of radioactivity can be obtained by direct plating of soluble samples which are as good as those obtained by combustion before counting—with a considerable saving of time. One method of obtaining reproducible direct glass plates involves wiping the plates with a trace of detergent before preparation of the sample (Gordon, Virgona, and Numerof, *Analyt. Chem.*, in the press).

The author is indebted to the British Empire Cancer Campaign and the American Cancer Society for a British–American Exchange Fellowship (1950—1951).

Organic Chemistry Department, Imperial College of Science and Technology, S. Kensington, London, S.W.7.
[Present address : Squibb Institute for Medical Research, New Brunswick, New Jersey, U.S.A.] [*Received, September 15th*, 1953.]

2-*Acetamido*-7-*methoxyfluorene.*

By John H. Weisburger and Elizabeth K. Weisburger.

[Reprint Order No. 4692.]

2-Acetamido-7-hydroxyfluorene, although a metabolite of the carcinogen 2-acetamidofluorene (Bielschowsky, *Biochem. J.*, 1945, **39**, 287; Weisburger *et al.*, *Fed. Proc.*, 1953, **12**, 287), is itself not carcinogenic (Bielschowsky, *Brit. Med. Bull.*, 1947, **4**, 382; Hoch-Ligeti, *Brit. J. Cancer*, 1947, **1**, 391). A similar situation occurs with 8-hydroxy-3 : 4-benzopyrene (Cook and Schoental, *ibid.*, 1952, **6**, 400), but 8-methoxy-3 : 4-benzopyrene is as active as 3 : 4-benzopyrene. We have therefore prepared 2-acetamido-7-methoxyfluorene for biological test; the procedures for preparation of the intermediates are improvements on those previously recorded (Ruiz, *Anal. Asoc. Quím. Argentina*, 1928, **16**, 170; Bielschowsky, *loc. cit.*, 1945; Goulden and Kon, *J.*, 1945, 930; Gutmann, *J. Amer. Chem. Soc.*, 1952, **74**, 836).

Experimental.—*2 : 7-Dinitrofluorene.* Fluorene was dinitrated as described by Courtot and Moreaux (*Compt. rend.*, 1943, **217**, 453) with this modification : The insoluble 2 : 7-dinitro-isomer was filtered off on a sintered-glass funnel from the warm reaction mixture, boiled in glacial acetic acid (2 l./100 g.) for 1 hr., and filtered off hot. This process was repeated twice to leach out any 2 : 5-isomer. The resulting material melted at 340° (block).

2-Amino-7-nitrofluorene. This compound was prepared by Cislak and Hamilton's method (*J. Amer. Chem. Soc.*, 1931, **53**, 746). Best yields (80—90%) resulted when the hydrogen sulphide was bubbled into the mixture at a fast rate and the reaction time limited to 2 hr. The toluene-*p*-sulphonamide sintered at 202° but melted at 215—215·5° after chromatography on alumina and recrystallisations from benzene and acetic acid (Found : C, 62·9; H, 4·35; N, 7·5. Calc. for $C_{20}H_{16}O_4N_2S$: C, 63·1; H, 4·2; N, 7·4%). Bell and Mulholland (*J.*, 1949, 2020) reported m. p. 202°.

2-Toluene-p-sulphonamido-7-aminofluorene. Reduction of the nitro-compound (2 g.) by zinc dust (4 g.) and calcium chloride (1 g.) in refluxing 80% ethanol (120 ml.) for 3 hr. gave a *product* (1·3 g.), m. p. 160—165°. Two recrystallisations from 50% ethanol raised the m. p. to 170—171° (Found N, 8·1. $C_{20}H_{18}O_2N_2S$ requires N, 8·0%).

2-Acetamido-7-hydroxyfluorene. 2-Amino-7-nitrofluorene (59 g.), dissolved in acetic acid (660 ml.) and 10N-sulphuric acid (155 ml.) and cooled, was diazotised with sodium nitrite (22 g.) in water (33 ml.). Urea (5·5 g.) in water (22 ml.) and cold 2·5N-sulphuric acid (650 ml.) was added after 1 hr. The suspension was added in portions to a boiling, mechanically stirred mixture of xylene (440 ml.) and 2·1N-sulphuric acid (1700 ml.) (the xylene prevented separation of tars), and the mixture boiled for 30 min. longer and then cooled. Yellow granules of *2-hydroxy-7-nitrofluorene* (59 g.), m. p. 239—246°, were obtained. Samples crystallised from xylene, acetic acid, ethanol, or dioxan melted at 248—250° (cf. Bielschowsky, *loc. cit.*, 1945).

Reduction to the amine and acetylation, essentially by Bielschowsky's method, gave *2-acetamido-7-hydroxyfluorene* (48 g.), m. p. 230—232° (transition pt. 216°) (Found: C, 75·4; H, 5·4; N, 5·8. Calc. for $C_{15}H_{13}O_2N$: C, 75·3; H, 5·5; N, 5·9%). The ultra-violet absorption, determined in ethanol (5 mg./l.) on a Cary automatic recording instrument, showed: min., 246 mμ (ε 1100); max. 293 mμ (ε 29,800); infl. 326 mμ (ε 11,500). The *acetoxy*-derivative, obtained by reaction with acetic anhydride (8 ml./1 g.) and fused sodium acetate (0·3 g./g.), melted at 137° after crystallisation from benzene and benzene–light petroleum (Found: C, 70·9; H, 5·7; N, 4·4; Ac, 30·8. $C_{17}H_{15}O_3N$ requires C, 70·9; H, 5·4; N, 5·0; Ac, 30·5%).

2-Acetamido-7-methoxyfluorene. 2-Acetamido-7-hydroxyfluorene (35·2 g.) in 1·1N-potassium hydroxide (530 ml.) was methylated at 10° with methyl sulphate (40 ml.), then stirred while being allowed to warm to 30°. After 2 hr. methyl sulphate (8 ml.) and solid potassium hydroxide (10 g.) were added and stirring continued for another hour. The precipitated material (32·5 g.), m. p. 199—201°, was filtered off and washed with water until the washings were neutral. A small amount (0·9 g.) of impure starting material was recovered from the filtrate by acidification.

The product was dissolved in hot ethanol (1250 ml.) (3 g. of Norit); concentration of the filtrate to about 700 ml. afforded the *ether* as shiny leaflets (24 g.), m. p. 204—205°. A sample (1·43 g.), recrystallised from 65% ethanol (75 ml.), had m. p. 204—206° (1·25 g.) Found: C, 75·5; H, 6·2. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). The ultra-violet absorption (8 mg./l.; EtOH) showed: min. 244 mμ (ε 1580), max. 293 mμ (ε 29,500); infl. 280 (ε 25,300) and 324 mμ (ε 11,500). Hydrolysis with 1 : 1 ethanol–concentrated hydrochloric acid gave 2-amino-7-methoxyfluorene, identical with that obtained by reduction of the nitro-compound (see below).

2-Methoxy-7-nitrofluorene. To a refluxing solution of 2-hydroxy-7-nitrofluorene (1·16 g.) in 0·4N-potassium hydroxide (35 ml.) and methanol (10 ml.) methyl sulphate (1 ml.) in methanol (5 ml.) was added with stirring. After 15 min. 2·3N-potassium hydroxide (6 ml.), methanol (10 ml.), and methyl sulphate (1·5 ml.) were added and the mixture was refluxed for 2·5 hr. The volume was reduced by approx. one-half and the solution was diluted with water to 100 ml. and cooled. The resulting precipitate was filtered off and washed until neutral, yielding a yellow powder (1·04 g.), m. p. 204—209°. From the acidified filtrate starting material (151 mg.), m. p. 244—248°, was recovered. The *product*, purified by passage in benzene through alumina, (yield, 610 mg.; m. p. 214—218°), crystallised from acetic acid as lemon-yellow needles (515 mg.), m. p. 216—219° (Found: C, 69·9; H, 4·8. $C_{14}H_{11}O_3N$ requires C, 69·7; H, 4·6%).

2-Amino-7-methoxyfluorene. A mixture of the nitro-derivative (502 mg.), zinc dust (1·7 g.), calcium chloride (140 mg.), and 80% ethanol (24 ml.) was refluxed with stirring for 2 hr., then filtered with suction into concentrated hydrochloric acid (1 ml.). This solution was boiled down to a small volume and cooled; the crystalline precipitate was filtered off and washed with 3N-hydrochloric acid. The yellowish solid was refluxed briefly in 0·06N-hydrochloric acid (50 ml.), and the solution was filtered hot. The colourless filtrate was made alkaline with ammonia, giving a white precipitate of the *amine* (287 mg.), m. p. 189—190° (Found: C, 79·5; H, 6·2. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2%). The acetyl derivative (prepared by acetic anhydride in benzene) had m. p. 205—206° unchanged by crystallisation.

The authors are indebted to Mr. James Williams and Miss Rita McCallum for the microanalyses.

National Cancer Institute, National Institutes of Health, Public Health Service,
U.S. Department of Health, Education and Welfare,
Bethesda 14, Maryland, U.S.A.

[*Received, October 3rd*, 1953.]

2 : 3-*Dimethyl*-1 : 4-*naphthaquinol Bis*(*dihydrogen Phosphate*).

By D. H. Marrian.

[Reprint Order No. 4708.]

Since the compound named in the title appeared to possess interesting biological properties (cf., *e.g.*, Mitchell and Simon-Reuss, *Brit. J. Cancer*, 1952, **6**, 317), its preparation and characterisation are described. All evaporations took place *in vacuo* in nitrogen.

Experimental—2 : 3-Dimethyl-1 : 4-napthaquinone (Kruber, *Ber.*, 1929, **62**, 3046) was shaken in methyl alcohol with hydrogen in the presence of reduced platinum oxide. The quinol obtained on evaporation was phosphorylated by the procedure described by Roche Products Ltd. (B.P. 593,480; see also Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, 1948, **3**, 263). 2 : 3-*Dimethyl*-1 : 4-*naphthaquinol di*(*barium phosphate*) *pentahydrate* crystallised in colourless prisms when its aqueous solution was heated to 90° in the water-bath with stirring. The salt was filtered off hot, washed with a little hot water, alcohol, and ether, and dried *in vacuo* (yield 77%) (Found, in material dried at room temperature: C, 20·0; H, 2·7; P, 8·55; loss at 120° *in vacuo*, 11·6. $C_{12}H_{10}O_8P_2Ba_2,5H_2O$ requires C, 20·4; H, 2·8; P, 8·75; $5H_2O$, 12·7%).

The barium salt (17·2 g.) was added to a solution of sodium sulphate (15·6 g. of decahydrate) in water (80 ml.) and shaken in the cold room overnight. The solution was filtered with the aid of "Hyflo" and gradually treated with 2 volumes of alcohol. The crystalline precipitate was filtered off, and washed once with aqueous alcohol (33% of EtOH), once with alcohol, and once with ether. 2 : 3-*Dimethyl*-1 : 4-*naphthaquinol bis*(*disodium phosphate*) formed colourless hydrated needles after drying off *in vacuo*. (13·4 g., 69%) (Found, in material dried in *vacuo* C, 18·2; H, 6·2; P, 7·15; loss at 60° *in vacuo*, 46·7. $C_{12}H_{10}O_8P_2Na_4,20H_2O$ requires C, 18·1; H, 6·3; P, 7·8; $20H_2O$, 45·2%).

2 : 3-*Dimethyl*-1 : 4-*naphthaquinol bis*(*dihydrogen phosphate*) was obtained by passing a solution of the dibarium salt through a column of Zeo-Karb 215 (H form). The colourless solution was evaporated, leaving a colourless solid which recrystallised from a little hot water as prisms, m. p. 260° (decomp.) (Found, in material dried at room temperature: C, 39·5; H, 4·1; P, 17·3%; equiv., 83·5. $C_{12}H_{14}O_8P_2,H_2O$ requires C, 39·4; H, 4·4; P, 16·9%; equiv., 91·5).

In 0·01N-hydrochloric acid the above compounds show maxima at 230—231 (ε 64,200) and 290—291 mμ (ε 5450) (measured on a Unicam S.P. 500 spectrophotometer). They may be quickly characterised by the following ratios of their absorptions at the wave-lengths (mμ) stated (pH2): 250/260 = 0·61; 280/260 = 2·50; 290/260 = 2·68; 310/260 = 1·13.

The author is grateful to Roche Products, Welwyn Garden City, Herts, and especially to Dr. F. Bergel and Dr. A. L. Morrison for their interest.

Department of Radiotherapeutics,
The University, Cambridge.

[*Received, October 7th*, 1953.]

Tetramethylammonium Amalgam.

By G. B. Porter.

[Reprint Order No. 4711.]

Tetramethylammonium amalgam was first isolated by McCoy and Moore (*J. Amer. Chem. Soc.*, 1911, **33**, 273), who reported that the organic ion NMe_4^+ displaces from aqueous solution Cu^{2+}, NH_4^+, Na^+, and K^+, and to a slight extent Rb^+ and Cs^+, that the amalgam decomposes rapidly (with inflation) above 0°, one of the products being trimethylamine, and that it reacts violently with water, forming hydrogen, black colloidal mercury, and tetramethylammonium hydroxide. By filtering off and weighing the colloidal mercury and titrating the filtrate with standard hydrochloric acid, they estimated the ratio Hg : NMe_4 for different samples. This ratio was not constant and gave no definite indication of compound formation.

The amalgam has now been prepared by a similar method and the above observations have been confirmed. It was thought that if free methyl radicals are liberated during thermal decomposition, these should be detectable under suitable conditions: $\cdot NMe_4 \longrightarrow NMe_3 + Me\cdot$. By using Paneth's "rapid flow" technique (*Ber.*, 1929, **62**, 1335) with tellurium mirrors (Rice and Glasebrook, *J. Amer. Chem. Soc.*, 1934, **56**, 2472), minute

concentrations of methyl radical were detected in the products of dissociation under reduced pressure.

Pure dry nitrogen was passed at 2 mm. pressure over the frozen amalgam (containing traces of the alcohol used in preparation) and through a long quartz tube (50 × 0·5 cm.), in which a tellurium mirror was condensed at *A* (the mouth of the tube). The amalgam was allowed to melt and decompose, and the tube was heated with a micro-burner (non-luminous flame) at *C* (about 40 cm. from *A*), where a faint, translucent white deposit was formed. When the tube was heated at *B* (about 30 cm. from *A*), another faint deposit appeared there, and the methyl produced at *B* began to remove the mirror at *C*. The mirrors at *B* and *C* were tested for tellurium and mercury; only the former was found. The only product found in the cold traps after each experiment was an alcoholic solution of trimethylamine.

Experimental.—The amalgam was prepared, in an apparatus similar to that described by McCoy and Moore (*loc. cit.*), by electrolysis of a solution of 5 g. of recrystallised tetramethylammonium chloride in 100 ml. of absolute alcohol at −15° (CO_2–acetone) with a current of 0·4 amp. for 15 min., between a silver anode and a redistilled mercury cathode. The product was removed through a wide-bore tap beneath the electrolytic cell, after excess of mercury had been run off, and stored at −78°.

The amalgam softens at −28° to a semi-solid paste, and is fairly stable at 0° when freshly prepared, but after it has been kept for a few days it begins to decompose at the m. p. and the decomposition is usually complete at 0°. It is difficult to remove the last traces of alcohol, with which it slowly reacts.

It was not possible to determine the properties of the amalgam in more detail (*e.g.*, electrode potential), because of its instability and variable composition.

The author thanks Professor E. C. Baughan for advice and help.

Royal Military College of Science,
Shrivenham, Wilts.

[*Received, October 8th,* 1953.]

The Addition of Some Acyl Hypobromites to Allyl Bromide.

By W. G. H. Edwards and R. Hodges.

[Reprint Order No. 4713.]

Israel, Tuck, and Soper (*J.*, 1945, 548) postulated the formation of acetyl hypobromite in the bromination of anisole by *N* : 2 : 4 : 6-tetrabromoacetanilide in acetic acid solution. Bromination of allyl bromide by the same reagents gave rise to an acetate $C_5H_8O_2Br_2$ (Mitchell and Soper, unpublished), and when trichloroacetic acid was replaced by acetic acid in this reaction, which was catalysed by pyridine, we obtained a mixture of a dibromopropyl trichloroacetate and a dibromopropanol.

When pre-formed acetyl, butyryl, and benzoyl hypobromites were added to allyl bromide, 2 : 3-dibromopropyl esters were isolated in yields of 60—85%. The products were identified by comparison of their infra-red spectra with those of authentic specimens, and, after catalytic debromination with hydrogen and palladised strontium carbonate, with the spectra of propyl esters previously reported (Edwards and Hodges, *J.*, 1953, 3427). The nature of the products was the same in the presence or absence of peroxides, and whether carbon tetrachloride or nitrobenzene was used as solvent.

Abbott and Arcus (*J.*, 1952, 1516) showed that 2-bromo-1-phenylethyl acetate (I) was produced by addition of acetyl hypobromite to styrene. We extended this reaction to *p*-methylstyrene and benzoyl hypobromite, but were able to isolate in a pure state only one product, which appeared to be a benzoate, $C_{16}H_{14}O_2$. This probably has the structure (II), being formed from 2-bromo-1-*p*-tolylethyl benzoate by loss of hydrogen bromide.

(I) $CH_2Br{\cdot}CHPh{\cdot}OAc$ $C_6H_4Me{\cdot}C(OBz){:}CH_2$ (II)

Experimental.—Bromination of allyl bromide with N : 2 : 4 : 6*-tetrabromoacetanilide.* To a solution of *N* : 2 : 4 : 6-tetrabromoacetanilide (22·6 g.) in chloroform (100 c.c.) were added trichloroacetic acid (24·0 c.c. of a 2·08M-solution in chloroform), pyridine (4·05 c.c.), and allyl bromide (4·3 c.c.). After 1½ hr., the precipitated tribromoacetanilide was filtered off, the chloroform removed by distillation, and the residue fractionally distilled under reduced pressure.

The fraction of b. p. 100°/1 mm. (1·5 g.) was redistilled for determination of its infra-red spectrum (chief maxima at 7·5, 8·7, 9·0, 9·8, 11·8, and 13·3 μ, with a band at 2·8 μ characteristic of the OH group of 2 : 3-dibromopropanol).

Reaction of acyl hypobromites with allyl bromide. (1) 2 : 3-Dibromopropyl butyrate. Silver butyrate (19·5 g., 0·12 mole) was suspended in dry carbon tetrachloride (250 c.c.), and about 50 c.c. of the solvent were evaporated to remove water. The cooled suspension was treated gradually with shaking at −10° with bromine (5·12 c.c., 0·1 mole), and shaking was continued until the colour of the bromine had faded to a pale yellow (3 min.). To the resulting solution of butyryl hypobromite was added at once pure allyl bromide (8·43 c.c., 0·1 mole), the mixture was shaken for 10 min., and the silver salts removed by filtration. The filtrate was shaken with saturated sodium hydrogen carbonate solution, washed with water, dried (Na_2SO_4), and evaporated. The residue was distilled under reduced pressure, and afforded 2 : 3-dibromopropyl butyrate, b. p. 118°/6·5 mm. (24·6 g., 85%).

(2) 2 : 3-Dibromopropyl benzoate and acetate. These were similarly prepared from silver benzoate and acetate respectively. 2 : 3-Dibromopropyl benzoate had b. p. 165°/3 mm., and the acetate, b. p. 68°/3 mm.

Addition of benzoyl hypobromite to p-*methylstyrene.* In the above method, silver benzoate (0·12 mole) and *p*-methylstyrene (0·1 mole) were used in place of silver butyrate and allyl bromide. Distillation of the addition product under reduced pressure gave a yellow oil, b. p. 150—170°/0·2 mm., which deposited crystals. From ethanol these formed colourless needles, m. p. 96° (Found : C, 80·5; H, 6·0. Calc. for $C_{16}H_{14}O_2$: C, 80·65; H, 5·9%). The infra-red absorption spectrum showed strong bands at 5·8, 7·8, and 9·0 μ, indicating the presence of a benzoate group.

The authors express their appreciation of the interest and advice of Professor F. G. Soper during the investigation, and thank Dr. A. D. Campbell for microanalyses. The assistance of the Mellor Fund is gratefully acknowledged.

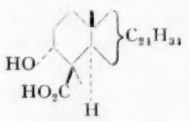
OTAGO UNIVERSITY, DUNEDIN, NEW ZEALAND. [*Received, October 10th,* 1953.]

Effect of Solvent on the Optical Rotation of Some Steroid α-Ketols.

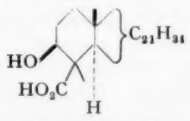
By J. K. NORYMBERSKI.

[Reprint Order No. 4768.]

BARTON and E. R. H. JONES (*J.*, 1944, 659) postulated intramolecular hydrogen bonding of α- and β-boswellic acid and their esters to account for the deviation from standard values of observed molecular-rotation increments on esterification and oxidation of the hydroxyl group. Similar rotatory anomalies may be expected for other compounds which fulfil the electronic and steric requirements for chelation. Furthermore, since solvents can interfere with the intramolecular hydrogen bond of the solute by, for instance, acting as hydrogen donors or acceptors, the optical rotations of chelated compounds may be greatly influenced by solvent. An anomalous solvent effect has now been found for a group of steroid α-ketols, including 17α-hydroxy-20-keto-steroids which were recently shown (R. N. Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820) to exhibit spectroscopic properties characteristic of chelated systems.



α-Boswellic acid.



β-Boswellic acid.

(Configuration of the carboxyl group in α-boswellic acid according to Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 2321. The molecular fragments summarily represented by $C_{21}H_{34}$ are not identical for the two isomeric acids.)

Rotations of the compounds (I)—(VI) (see Table) were taken in chloroform, dioxan, acetone, and ethanol, *i.e.*, in the solvents most commonly used for steroids. The maximum changes of $[M]_D$ with solvent found for (I), (III), (IV) and (V) were 120°, 138°, 147°, and 145°, respectively, values which greatly exceed the normally observed maximum variation of *ca.* 40° (cf. Josephson, *Biochem. J.*, 1935, **29**, 1484; Plattner and Heusser, *Helv. Chim. Acta*, 1944, **27**, 748; Barton, *J.*, 1946, 1116; Barton and Brooks, *J.*, 1949, 2596). The

$[M]_D$ values of 3β : 5α-diacetoxycholestan-6-one (II) and 3α : 17α-diacetoxypregnane-11 : 20-dione (VI), in which the hydrogen bonding has been suppressed by acetylation of

Substance	$[M]_D$ in : $CHCl_3$	$C_4H_8O_2$	$COMe_2$	EtOH
3β-Acetoxy-5α-hydroxycholestan-6-one (I)	−263° (−257) [a]	−219°	−143°	−228° *
3β : 5α-Diacetoxycholestan-6-one (II)	− 70 (− 77) [a]	− 60	− 73	− 98
21-Acetoxy-17α-hydroxypregn-4-ene-3 : 11 : 20-trione (III)	+919 (+879) [b]	+885 (+852) [c]	+781 (+750) [b]	+898 *
3α : 17α-Dihydroxypregnane-11 : 20-dione (IV)	+132	+247	+235 (+239) [d]	+279
3α-Acetoxy-17α-hydroxypregnane-11 : 20-dione (V)	+222	+351	+309 (+327) [d]	+367
3α : 17α-Diacetoxypregnane-11 : 20-dione (VI)	+195 (+202) [c]	+220	+229	+201
$\Delta_1(5\alpha)$ for (I) ⟶ (II)	+193	+159	+ 70	+130
$\Delta_1(3\alpha)$ for (IV) ⟶ (V)	+ 90	+104	+ 74	+ 88
$\Delta_1(17\alpha)$ for (V) ⟶ (VI)	− 27	−131	− 80	−166

* With addition of chloroform. [a] Schenck, *Z. physiol. Chem.*, 1936, **243**, 119. [b] Kritchevsky, Garmaise, and Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 483. [c] Turner, *ibid.*, 1953, **75**, 3604. [d] Sarett, *ibid.*, 1948, **70**, 1454. [e] Huang-Minlon, Wilson, Wendler, and Tishler, *ibid.*, 1952, **74**, 5394.

the ketolic hydroxyl group, vary with solvent by not more than 38° and 34°, respectively, *i.e.*, within the normal range. The rotation increments for (I) ⟶ (II), (IV) ⟶ (V), and (V) ⟶ (VI) [$\Delta_1(5\alpha)$, $\Delta_1(3\alpha)$, and $\Delta_1(17\alpha)$, respectively] can be calculated from rotations taken either in the same solvent or in different solvents. In the former case the range of variation with solvent is +70° to +193° for $\Delta_1(5\alpha)$, +74° to +104° for $\Delta_1(3\alpha)$ (standard value for 3α-hydroxy-5β-steroids is +83°; cf. Barton, *loc. cit.*), and −27° to −166° for $\Delta_1(17\alpha)$; in the latter case it is +45° to +203° for $\Delta_1(5\alpha)$, −55° to +255° for $\Delta_1(3\alpha)$, and +7° to −172° for $\Delta_1(17\alpha)$.

It is apparent that an anomalous solvent effect must be taken into consideration when applying the method of molecular-rotation differences to chelated compounds: when structural changes are studied at a site far removed from the chelated system, as in (IV) ⟶ (V), the $[M]_D$ increments must be computed from rotations taken in the same solvent, though it does not appear to matter which particular solvent is chosen. When the structural change involves the chelated system itself, as in (I) ⟶ (II) and (V) ⟶ (VI), it is essential to carry out all measurements in one solvent only. Failure to observe these precautions may lead to fortuitous and misleading results. An illustration is provided by Turner's recently attempted correlation (*loc. cit.*) of Δ_1 values for 17-hydroxypregnan-20-ones with their configuration at $C_{(17)}$. A compilation of relevant rotational data led Turner to conclude that acetylation of 17α-hydroxypregnan-20-ones gives rise to a large negative (>−100°) $[M]_D$ shift, while in the 17-epimeric series the shift is either small or positive. The cited examples include the increment of −125° for (V) ⟶ (VI) calculated from the rotations of (V) in acetone and of (VI) in chloroform; the same increment when computed from the rotations of (V) in chloroform and of (VI) in acetone (see Table) is +7°, *i.e.*, within the range allegedly characteristic for the 17α-pregnane series.

Experimental.—All specimens were dried in high vacuum for 3—6 hr. at 100—120°. M. p.s were determined on a Kofler stage. Rotations were taken at 16—18° in a 1-dm. micro-tube: for each compound the four successive sets of rotations refer respectively to solutions in chloroform, dioxan, acetone, and ethanol except where ethanol–chloroform is specified for the last.

3β-*Acetoxy*-5α-*hydroxycholestan*-6-*one* (I).—3β : 5α-Dihydroxycholestan-6-one was prepared from cholesterol *via* cholestane-3β : 5α : 6β-triol as described by Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, 1949, **71**, 3938), and acetylated with acetic anhydride in pyridine at 18°. The crude acetate, recrystallised from acetone, had m. p. 231—233°, $[\alpha]_D$ −56°, −57·5°, −58°, −57·5°, −56·5° (*c*, 0·61, 0·92, 1·20, 1·96, 3·73), −47·5° (*c*, 0·88), −31° (*c*, 0·58), −49·5° (*c*, 0·81 in ethanol–chloroform; 80 : 20, v/v).

3β : 5α-*Diacetoxycholestan*-6-*one* (II).—This compound was prepared from the dihydroxy-ketone by Fieser and Rajagopalan's procedure (*loc. cit.*); crystallised from methanol, it had m. p. 171—173°, $[\alpha]_D$ −14° (*c*, 2·30), −12° (*c*, 1·67), −14·5° (*c*, 2·09), −19·5° (*c*, 1·68).

21-*Acetoxy*-17α-*hydroxypregn*-4-*ene*-3 : 11 : 20-*trione* (III).—The commercial preparation

(Merck & Co., Inc.) was recrystallised from ethanol and then had m. p. 238—240°, $[\alpha]_D$ +228° (*c*, 1·01), +220° (*c*, 0·94), +194° (*c*, 0·66), +223° (*c*, 0·52 in ethanol–chloroform; 80 : 20, v/v).

3α : 17α-*Dihydroxypregnane*-11 : 20-*dione* (IV).—A specimen supplied by Messrs. N. V. Organon (Oss) was recrystallised from acetone and then had m. p. 202—204°, $[\alpha]_D$ +38° (*c*, 1·56), +71° (*c*, 1·46), +67·5° (*c*, 1·06), +80° (*c*, 0·71).

3α-*Acetoxy*-17α-*hydroxypregnane*-11 : 20-*dione* (V).—This compound was obtained from the dihydroxy-ketone (IV) by acetylation with acetic anhydride in pyridine at 18° and had m. p. 203—204° after crystallisation from acetone–light petroleum, and $[\alpha]_D$ +57° (*c*, 1·40), +90° (*c*, 1·29), +79° (*c*, 1·05), +94° (*c*, 0·87).

3α : 17α-*Diacetoxypregnane*-11 : 20-*dione* (VI).—This compound was prepared by Turner's general procedure (*ibid.*, 1953, **75**, 3489) : 3α-acetoxy-17α-hydroxypregnane-11 : 20-dione (200 mg.) in glacial acetic acid (10 c.c.) and acetic anhydride (2 c.c.) was treated with toluene-*p*-sulphonic acid (200 mg.) and left overnight at 18°. The solution was diluted with water, and the product extracted with ether. Two crystallisations from ether–light petroleum furnished needles, m. p. 201—203°, $[\alpha]_D$ +45° (*c*, 1·13), +51° (*c*, 0·94), +53° (*c*, 1·06) +46·5° (*c*, 0·88) (Found : C, 69·3; H, 8·3. Calc. for $C_{25}H_{36}O_6$: C, 69·4; H, 8·4%).

This work was done during the tenure of an Empire Rheumatism Council Research Fellowship.

RHEUMATISM RESEARCH UNIT,
NETHER EDGE HOSPITAL, SHEFFIELD, 11. [*Received, November 4th*, 1953.]

The Reaction of Phenyl-lithium with Azobenzene.

By P. F. HOLT and B. P. HUGHES.

[Reprint Order No. 4847.]

WITTIG ("Newer Methods of Preparative Organic Chemistry," Interscience Publ., Inc., New York, 1948, p. 590, footnote) states that phenyl-lithium reacts with azobenzene to give triphenylhydrazine and hydrazobenzene but does not mention the conditions of the reaction. Gilman and Baillie (*J. Org. Chem.*, 1937, **2**, 84) using stated conditions could find no triphenylhydrazine but obtained diphenyl and hydrazobenzene. Beringer, Farr, and Sands (*J. Amer. Chem. Soc.*, 1953, **75**, 3984) confirmed the findings of Gilman and Baillie and used them to deduce the course of a reaction between phenyl-lithium and nitrous oxide which yielded lithium benzenediazoate, azobenzene and triphenylhydrazine. They argued that, since azobenzene and phenyl-lithium do not give triphenylhydrazine, the triphenylhydrazine produced in the last reaction must be formed by the action of phenyl-lithium on the lithium benzenediazoate rather than on the azobenzene.

We find that either triphenylhydrazine or hydrazobenzene may be formed.

If azobenzene (1 mol.) is stirred with phenyl-lithium (2 mol.) in ether for 40 hours as described by Gilman and Baillie, hydrazobenzene is formed. The following procedure gives triphenylhydrazine : Phenyl-lithium (1·6 g.) in dry ether (20 ml.) is added to azobenzene (3·6 g.) in dry ether (30 ml.) under nitrogen. The mixture is stirred for 5 minutes, then saturated ammonium chloride solution is added. The residue left on evaporation of the ethereal layer, when washed with light petroleum and recrystallised from ethanol, gives triphenylhydrazine, m. p. 141—142° (decomp.) (it yields *N*-phenylbenzidine, m. p. 136—137°, with hydrochloric acid in warm aqueous ethanol). The mother-liquor contains mainly hydrazobenzene.

The yield of triphenylhydrazine varies with the reaction temperature; it is 10% at 20° or 20% at 0°. The higher yield with decreased temperature conforms with the formation of triphenylhydrazine under the initial conditions which Beringer *et al.* used (−20° for 2 hr.). Gilman and Baillie considered that the hydrazobenzene was unlikely to be formed by the action of phenyl-lithium on the intermediate *N*-lithiotriphenylhydrazine because triphenylhydrazine does not react with phenylmagnesium bromide (Gilman and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 2004) which they considered analogous to phenyl-lithium. We find, moreover, that there is no reaction between triphenylhydrazine and phenyl-lithium under the conditions of the experiment. However this argument assumes that the reactivity of *N*-lithiotriphenylhydrazine is similar to that of triphenylhydrazine itself, which may be untrue.

We are indebted to Imperial Chemical Industries Limited, Paints Division, for a grant to one of us (B. P. H.).

THE UNIVERSITY, READING. [*Received, November 28th*, 1953.]

OBITUARY NOTICES.

L. M. CLARK.

1897—1953.

Dr. L. M. Clark was born on January 24th, 1897, at Ashover, Derby, and educated at the High School, Nottingham, and Sidney Sussex College, Cambridge. He obtained an honours degree in chemistry in 1921, and a Ph.D. of London University in 1923 for research work carried out in Cambridge 1921—23.

Before going to Cambridge Dr. Clark was employed for 1½ years at the National Shell-filling Factory at Chilwell. On leaving the University he took an appointment in the Metallurgical Department of the National Physical Laboratory, Teddington. In 1928 he joined the Research Department of the Alkali Division of Imperial Chemical Industries Limited at Winnington, Northwich, as a research chemist. In 1933 he became Deputy Manager of the Technical Sales Service Department, but on the outbreak of the war in September, 1939, he returned to the Research Department and was in charge of work on a succession of problems being tackled at Winnington on behalf of the Government. During this period he was appointed Assistant Research Manager. In 1949 he returned to the Technical Sales Service Department as its Head, a post he held until his death on September 26th, 1953.

His published scientific work led to the award by his University, Cambridge, at the end of 1949, of the degree of Doctor of Science.

He leaves a widow, herself a Cambridge graduate, and two daughters, the elder of whom took her degree in Geography at Cambridge University.

Dr. Clark was very popular with his colleagues, and had a wide circle of friends in industry and at Winnington. His post caused him to travel frequently in the United Kingdom, and he also visited Russia, South Africa, the United States of America, and Canada. His two great hobbies were fishing and bridge.

E. A. Cooke.

WILLIAM JACOB JONES.

1886—1952.

William Jacob Jones was born in Melbourne on St. David's Day, 1886. The only son of Evan and Ann Jones, he survived an attack of cholera at the age of seven, and the family then returned to Llanrwst, North Wales. When he was fourteen, he left the local Grammar School to enter his father's business, but continued his studies privately, and in two years passed the Matriculation and Intermediate examinations of the University of London. Proceeding to the University College of North Wales, Bangor, in 1905, he graduated with first class honours in chemistry in 1908, and was awarded the Isaac Roberts research scholarship. He commenced research work under the direction of Professor K. J. P. Orton, and obtained the degree of M.Sc. (Wales). Their first papers dealt with the composition of bleaching powder. This work was followed by a study of the chlorination of anilides, to which Dr. Harold King has referred in the following terms: "In the years 1909 and 1910 there appeared a series of papers by Orton and Jones which marks an epoch in the study of the dynamics of halogenation of anilides. These communications are to be classed with the pioneering work of Harcourt and Esson on the application of the mass law. Although Orton was no expert mathematician, he had his Esson in the person of W. J. Jones. Jones and Orton showed that the conversion of chloroamines into nuclear-substituted anilides, a reaction considered by Chattaway and Orton to be an intramolecular process, was in reality an intermolecular one and could be summarised in this way:

$$Cl_2 + H{\cdot}Ar{\cdot}NHAc \rightleftharpoons \begin{cases} Cl{\cdot}ArNHAc + HCl & (a) \\ H{\cdot}Ar{\cdot}NClAc + HCl & (b) \end{cases}$$

A system made up from molecular proportions of *s*-tribromoacetanilide, hydrochloric acid, and acetylchloroamino-*p*-nitrobenzene in 90% acetic acid was found experimentally to contain 50%

of the chlorine originally present as chloroamine in the free state, whilst the calculated value was 60%. This was a brilliant demonstration of the correctness of the authors' views and of the application of the law of mass action."

Jones carried out further research at the University of Manchester with Lapworth (1910—1911), and at Leipzig with Le Blanc (1911—1912), and then returned to Manchester, where he obtained the degree of M.Sc. in 1913. Appointed lecturer in chemistry at Manchester University in the same year, he received the Doctorate of Science of the University in 1918 and was promoted senior lecturer in 1919. His early work with Lapworth was concerned with equilibria in esterification processes. This was followed by an investigation of the action of hydrogen cyanide on aldehydes and ketones, and in 1914 Jones published an important paper on the mechanism of cyanidion catalysis. He then turned his attention to the surface energy of solids and was able to formulate mathematically the influence of particle size on the solubility of barium sulphate, which had been demonstrated experimentally by Hulett. At this time one of his colleagues was J. R. Partington, and they collaborated in a theoretical study of the refractivities of gases. Other papers published by Jones during this period covered such subjects as the estimation of aniline, benzene, and nitrobenzene in commercial specimens, the properties of pyridine bases, the estimation of the methoxyl group (with J. T. Hewitt), a fractionating column with moving parts (with J. E. Myers), and the congelation of essential oils.

His work at Manchester was interrupted by war service. In 1914 he joined the Royal Welch Fusiliers as a Second Lieutenant, was promoted Lieutenant in 1915, and earned the 1914—1915 Star for service with the British Expeditionary Force in France and Flanders. He was seconded to the Ministry of Munitions in 1916, and was promoted Captain in 1919, a rank which he retained on completion of service.

After his appointment to the Chair of Chemistry at University College, Cardiff, in 1921, Professor Jones set his research students to work on a variety of problems among which may be mentioned the solubility of salts in organic solvents (with D. G. R. Bonnell), the photodecomposition of triphenylmethyl, organometallic compounds (with W. C. Davies, W. J. C. Dyke), addition reactions of the azomethine group (with D. Philpott), the action of chlorine on isoprene, viscosity of liquids, adsorption from solution, cohesive forces, and vapour pressure. Having become familiar with a particular field, Jones found pleasure in moving to new pastures, and it it to this trait that we must ascribe the wide variety and range of his interests in physical chemistry and in organic chemistry.

At Cardiff his great gifts as a teacher were much appreciated by his many students. His simple, direct approach and painstaking endeavour to simplify and explain even complicated problems was of considerable benefit to all, and especially to students of the biological sciences. Because he was at heart of a shy and retiring nature, he had little to say in the presence of strangers, but with those whom he knew well he was most affable and gave ample evidence of the wide scope of his reading. He had command of several languages and spoke Welsh and German fluently. He was an able mathematician and a keen amateur astronomer. It is reported in *Nature* that he observed and plotted the track of a daylight fireball over Scotland on Aug. 20, 1932.

Professor Jones expended considerable effort in the planning and furnishing of the new Tatem laboratories which were opened in 1927. The administrative duties of a large department entailed considerable labour, but correspondence was dealt with immediately, and replies were generally written in his own hand and invariably dispatched by return of post. The difficulties encountered during the period 1939—1945 were accentuated by the evacuation to Cardiff of a section of the Ministry of Supply and the chemistry departments of two London Colleges. The lack of laboratory space involved considerable reorganization of classes, and teaching became very arduous. With the initial difficulties smoothed away, Professor Jones once again served his country as an Officer in a Bomb Disposal Unit of the Royal Engineers. On completion of his service, he returned to his department, where he remained until his retirement in September, 1951. Alas, he was not to enjoy for long the rest he had so well earned. He died suddenly at his home in Cardiff on October 14, 1952, leaving a widow and three children.

S. J. H. O. Chard.
S. T. Bowden.

SIR THOMAS TAYLOR.

1895—1953.

SIR THOMAS TAYLOR, C.B.E., M.A., D.Sc., Principal of the University College of the South West, died suddenly on August 29th, 1953, while on holiday in Italy.

Thomas Weston Johns Taylor was born in 1895, the son of the late T. G. Taylor. His family was connected with the French wine industry and he spent a good deal of his boyhood in Bordeaux; to these early connections may be traced his knowledge of French and his cosmopolitanism. He was educted at the City of London School, a fact which made him *persona grata* with another eminent Old Citizen, the late W. H. Perkin, jun., in whose Department Taylor worked in Oxford. He went up to Brasenose in 1913 with an Open Scholarship in Natural Science. He was a pupil of F. D. Chattaway and worked with him for his first year in the old Queen's Laboratory. In 1914 he at once joined the Army and served throughout the war in the Essex Regiment; he was twice wounded in Gallipoli. After the war he returned to Oxford and took First Class Honours in Chemistry in 1920; in the same year he was elected to a Fellowship at Brasenose and was placed in charge of the chemistry teaching. He became a University Demonstrator in 1927. Owing to the nature of Part II of the Chemistry School in Oxford, he was required at once to plunge into research. He needed no urging and at once set to work in the field of nitrous acid chemistry. But before he had brought any of his major investigations to the stage of publication, his accurate and active mind had led to his intervention, with significant results, in two controversial topics of the time. The first was his experimental refutation, in a particular case, of the widely held view that strictly unimolecular reactions were caused by "radiation." The second was his resolution of the "Rivett Paradox," which made it appear that solid phases of invariable composition were thermodynamically impossible. His procedure was to go back to Gibbs's original work and to put it into simpler and more direct language, with the result that the problem vanished after a short Note in the *Journal* (*J.*, 1924, 2016).

As research pupils came along, his work on nitrous acid was speeded up. In the first of three papers (Taylor, Wignall, and Cowley, *J.*, 1927, 1923) he showed how comparatively stable solutions of nitrous acid could be prepared and preserved under a layer of medicinal paraffin, and with such solutions he was able to obtain evidence in support of his view that the equilibrium $2HNO_2 \rightleftharpoons N_2O_3 + H_2O$ is established. A further equilibrium $N_2O_3 \rightleftharpoons NO + NO_2$ tends to be set up but the concentration of nitric oxide cannot exceed a certain limit on account of its small solubility. In subsequent papers (*J.*, 1928, 1099, 1897) he showed that the rates of reaction of glycine, α-alanine, and β-alanine with nitrous acid probably follow a third-order equation, being proportional to the concentrations of "zwitter-ion," undissociated nitrous acid, and nitrite ion.

Quite early in his career Taylor became interested in oximes and in particular in their stereochemistry, which had assumed great importance in connection with the revolutionary views as to the mechanism of the Beckmann transformation necessitated by the work of Meisenheimer. Working with the monoximes of benzil, he began by showing (Taylor and Ewbank, *J.*, 1926, 2818) that in the β-oxime the hydroxyl and the carbonyl group are so situated that co-ordination (hydrogen bonding) can occur between them. This conclusion was supported (Taylor and Marks, *J.*, 1930, 2302) by solubility measurements and by studies of metallic derivatives of the α- and the β-monoxime (Taylor, *J.*, 1931, 2018). This work culminated in 1933 in the fundamental measurements, carried out in conjunction with L. E. Sutton (Taylor and Sutton, *J.*, 1931, 2190), on the electric dipole moments of the "*N*-ethers" of the two *p*-nitrobenzophenone oximes. These left very little doubt that the configurations of the oximes were in accordance with the Meisenheimer mechanism for the Beckmann transformation. The last possible loop-hole was closed in 1933 (Taylor and Sutton, *J.*, 1933, 63) with the determination of the electric dipole moments of the *p*-nitrobenzaldoximes.

Taylor's interest in stereochemical problems continued until the outbreak of war; his last paper (Taylor, Callow, and Francis, *J.*, 1939, 257) concerned the metallic derivatives of hydrazones and of the oxime-hydrazones.

Taylor collaborated with Professor Wilson Baker, at the time a Fellow of Queen's, in the revision of N. V. Sidgwick's great "Organic Chemistry of Nitrogen"; a considerable share of credit for the fact that the vigour and sparkle of the original suffered so little from the inevitable process of re-writing must be given to him. A useful contribution to chemical literature, distinguished for its comprehensiveness and lucidity, was his article on the

" Chemistry of proteins and related substances " in the Chemical Society's *Annual Reports for* 1937. He also edited the second volume of the English revision of " Richter–Anschütz."

In Oxford Taylor will be remembered for his vivid personality and his versatility. He was an admirable Tutor and an inspiring teacher. His interests ranged from bird-watching to modern French poetry, from music (he was an enthusiastic member of the Bach Choir) to travel, both in its more usual and in its less conventional forms. He used the award of a Rhodes Travelling Scholarship in 1931 to visit America. His knowledge of Europe and, in particular, of its localities specially remarkable for good wine and food, was extensive; he also thought nothing of a Long Vacation in Persia, Afghanistan, or the Galapagos islands. He and his wife made their home an envied centre of musical and literary life. He played little part in University administration, which is surprising considering his subsequent career. He served, however, on the Council of the Chemical Society from 1936 to 1939.

A few months after the outbreak of the World War in 1939 he seized an opportunity of being commissioned in the R.E. in a Chemical Warfare Section. He served for a short time at Porton, and then, until 1943, in charge of the Chemical Warfare Branch of the Middle East Command staff at Cairo, being mentioned in despatches. He was then transferred, as a civilian, to be first the Secretary and then the Director of the British Central Scientific Office at Washington, and in 1944 was selected to head the " Operational Research " Division on Lord Mountbatten's staff in Ceylon. He was made C.B.E. in 1946.

The end of the war found Taylor, as he confessed, out of touch with, and feeling little interest in, formal science and its teaching. He came back to Brasenose, but in 1946 was invited to become the first Principal of the University College of the West Indies. Chemistry lost by his acceptance of that invitation, but the influence he was thus enabled to exert in wider fields was more than a compensation. All his energy and " drive " as an organiser and negotiator, as well as his capacity for inspiring his academic collaborators with enthusiasm for his own educational ideals, were required for the task of bringing the new University College into actual existence and presiding over its functioning during the crucial earliest stage. By 1952, he could feel that this task had been essentially accomplished, and (wishing, as he put it himself, to return to this country, rather than to wait until he had to retire to it) he asked to be allowed to " hand over " to a successor. Coming back, he was appointed to succeed John Murray as Principal of the University College of the South West, at Exeter, and flung himself with undiminished vigour into his new duties. He was knighted in July 1952.

He married, in 1922, Rosamund Georgina, the younger daughter of Colonel T. E. J. Lloyd, C.B., of Plâs Tregayan, Anglesey.

D. Ll. Hammick.

H. K. LEWIS BOOKS ON THE CHEMICAL AND ALLIED SCIENCES

Scientific and Technical Books. :: Large Stock of Recent Editions. :: Foreign Books not in stock obtained under Special Licence. :: Catalogues on request.

LENDING LIBRARY — Scientific and Technical

ANNUAL SUBSCRIPTION FROM 25s. *PROSPECTUS FREE ON APPLICATION*

THE LIBRARY CATALOGUE containing classified Index of Authors and Subjects revised to December 1949. Pp. xii + 1152. To subscribers 17s. 6d. net. To non-subscribers 35s. net., postage 1s. 3d. Supplement 1950 to 1952. To subscribers 3s. net; to non-subscribers 6s. net; postage 6d.

BI-MONTHLY LIST OF NEW BOOKS AND NEW EDITIONS ADDED TO THE LIBRARY POST FREE TO SUBSCRIBERS REGULARLY

H. K. LEWIS & Co. Ltd., 136 Gower Street, London, W.C.1

Telephone: EUSton 4282 (7 lines)

ESTERS OF CHLORINATED ACETIC ACIDS

We are manufacturers of :-

MONOCHLOROACETATES

ETHYL, ISOPROPYL and BUTYL

DICHLOROACETATES

METHYL, ETHYL, ISOPROPYL and BUTYL

TRICHLOROACETATES

METHYL, ETHYL, ISOPROPYL, BUTYL and BENZYL

Samples and quotations from

KAYLENE BRAND

KAYLENE (CHEMICALS) LTD.

WATERLOO ROAD, LONDON, N.W.2

No. 3289 * * * * *

In the Eastman Organic Chemicals Catalogue No. 38, this refers to 1.10-PHENANTHROLINE, a rather expensive chemical at £4.6.0d. per gramme. However, there are thousands of others which you may need, probably very much cheaper, and a lot of them are in stock at Kirkby. Send your requirements for Eastman grade chemicals to :—

KODAK LIMITED
KIRKBY TRADING ESTATE
LIVERPOOL

—MANSFIELD OIL-GAS PLANT—

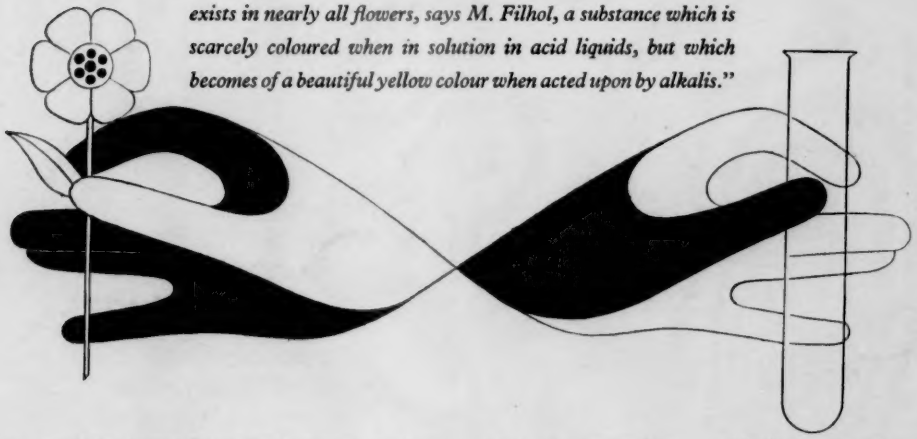
FOR LABORATORIES' GAS SUPPLY

Laboratories without a supply of gas should write for particulars of this Plant which produces gas in a simple manner from any cheap oil such as Solar Oil. . . . The gas produced has a calorific value of 1,350 B.T.U.'s per cubic foot, and is suitable for use with any appliance designed for use with coal gas and gives perfect oxidising and reducing flames.

MANSFIELD & SONS LTD
62 HAMILTON SQUARE, BIRKENHEAD

An examination by M. Filhol

"Vegetable Colouring Matters:—M. Filhol has been engaged in the examination of vegetable colouring matters, and has discovered some facts which he now publishes as briefly as possible, intending to give all the details in a longer memoir. There exists in nearly all flowers, says M. Filhol, a substance which is scarcely coloured when in solution in acid liquids, but which becomes of a beautiful yellow colour when acted upon by alkalis."



M. FILHOL'S DISCOVERIES were made nearly a hundred years ago. This early note of them appeared in the first volume of 'Chemical News,' published in 1860.

Natural dyes have long been superseded as indicators by the highly purified synthetic dye compounds used today for colorimetric measurements of hydrogen ion concentration, oxidation-reduction balance and adsorption capacity.

Theory and practice in these fields are explained in three B.D.H. booklets — 'pH Values,' 'The Colorimetric Determination of Oxidation-Reduction Balance' and 'Adsorption Indicators'— which may be obtained free on request.

LABORATORY **B·D·H** CHEMICALS

THE BRITISH DRUG HOUSES LTD. B.D.H. LABORATORY CHEMICALS GROUP POOLE DORSET
LC/IN6

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.